Medisch Spectrum Twente

Medical School Twente

Wetenschappelijk onderzoek MST 2022

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een santeon ziekenhuis

Wetenschappelijk onderzoek in Medisch Spectrum Twente

2022

Inhoudsopgave

Voorwoord

Voor u ligt de 14e editie van het jaarlijkse overzicht van de wetenschappelijke output van medewerkers van Medisch Spectrum Twente. Het betreft het jaar 2022. Dit jaaroverzicht wordt ook buiten MST verspreid onder huisartsen, apothekers, fysiotherapeuten en andere wetenschappelijke instellingen in de regio.

De publicaties zijn gegroepeerd op vakgroep of maatschap. Niet op volgorde van belangrijkheid maar alfabetisch. Hierbij is als criterium genomen dat de publicatie terug te vinden moet zijn op PubMed en de publicatiedatum moet ook in 2022 zijn. De zogenaamde "Epub Ahead of Print" artikelen komen in de volgende uitgave. Daarnaast worden ook peer-reviewed artikelen uit geïndexeerde en peer-reviewed Nederlandstalige tijdschriften opgenomen.

In 2022 zijn 383 unieke publicaties verschenen in peer-reviewed tijdschriften. Dit is bijna 15% meer dan 2021, en 2021 was al een absoluut topjaar! We produceren dus ruim één publicatie per dag. Wat opvalt is dat onderzoekers uit MST inmiddels veel publicaties hebben waar ze onderdeel zijn van een consortium.
De gemiddelde impact score van alle artikelen is bizar hoog met 9,9, weer een nieuw record voor MST. Daar moet wel een kanttekening bij geplaatst worden. Een aantal tijdschriften, zoals the Lancet hebben inmiddels een absurd hoge impact factor (202), hoogstwaarschijnlijk veroorzaakt door een aantal COVID artikelen. Dit jaar hebben we 2 keer in het absolute toptijdschrift New England Journal of Medicine gestaan, 3 keer in de Lancet, 4 keer in een subtijdschrift van de Lancet en 1 maal in Science en Nature. Door de extreem scheve verdeling is het realistischer om in plaats van de gemiddelde impact factor de mediane impact factor te presenteren. Die is ook erg hoog met 4,6.

Ook wordt per publicatie ook weergegeven in welk kwartiel het tijdschrift staat in de betreffende categorie. Indien meerdere categorieën van toepassing zijn wordt het hoogste kwartiel genomen. We publiceerden 54% in Q1, 28% in Q2, 12% in Q3 en 6% in Q4. Dat is nagenoeg identiek aan vorig jaar.
Qua promoties was 2022 een redelijk jaar met "maar" 6 promoties in MST. Dit heeft naar alle waarschijnlijkheid te maken met het feit dat veel mensen die hun promotie uit konden stellen dat ook gedaan hebben totdat er weer meer mogelijk was qua verdediging en festiviteiten vanwege Covid.

In deze uitgave vindt u per gepubliceerd artikel de impact factor van het tijdschrift en per vakgroep of maatschap de totale en gemiddelde impact factor score van alle gepubliceerde artikelen. Om een indruk te krijgen van de bijdrage van eigen onderzoek is ook een overzicht gegeven van het aantal artikelen waarbij een onderzoeker uit MST 1e, 2e of laatste auteur is.

Om de ontwikkeling te kunnen volgen zijn de ranglijsten van 2022 naast die van eerdere jaren weergegeven.

Ik wens u veel leesplezier toe,

Prof. dr. Job van der Palen
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Overzicht publicaties en de Top 3

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Unieke publicaties	191	212	245	226	216	240	232	239	334	383
Impact factor	4.38	4.03	5.06	4.70	4.47	5.64	6.12	5.79	6.48	9.88
Mediane impact factor							3.20	3.44	3.93	4.58

2019			2020			2021			2022		
Top 3: Aantal publicaties:											
1	Heelkunde	39	1	Cardiologie	40	1	Neurocentrum	52	1	Heelkunde	67
2	Neurologie	33	2	Med. School	29	2	Thoraxcentrum	47	2	Neurocentrum	52
3	Cardiologie	27	3	Neurocentrum	29	3	Heelkunde	43	3	Thoraxcentrum	47
Top 3: Totale impact factor score:											
1	Cardiologie	306	1	Cardiologie	433	1	Neurocentrum	442	1	Neurocentrum	713
2	Intensive care	197	2	Interne gnkd	169	2	Thoraxcentrum	346	2	Intensive care	647
3	Longziekten	148	3	MDL	145	3	Intensive care	307	3	Heelkunde	561
Top 3: Gemiddelde impact factor score:											
1	MDL	16.6	1	Oogheelkunde	17.7	1	Microbiologie	25.1	1	Intensive care	17.5
2	Intensive care	14.2	2	Radiotherapie	11.4	2	Radiologie	17.9	2	Interne gnkd	17.0
3	Cardiologie	7.7	3	Cardiologie	10.8	3	MDL	11.2	3	Radiologie	16.6
Top 3: Aantal publicaties als 1e, 2e of laatste auteur:											
1	Cardiologie	20	1	Neurocentrum	15	1	Neurocentrum	23	1	Heelkunde	18
2	Longziekten	17	2	Cardiologie	14	2	Thoraxcentrum	14	2	Neurocentrum	15
3	Neurologie	13	3	Med. School	10	3	Longziekten	10	3	Thoraxcentrum	12
3	Med. School	13									
Top 3: Totale impact factor score als 1e, 2e of laatste auteur:											
1	Cardiologie	178	1	Interne gnkd	63	1	Neurocentrum	85	1	Heelkunde	85
2	Longziekten	99	2	Neurocentrum	61	2	Thoraxcentrum	44	2	Klin. farmacie	78
3	Med. School	44	3	Cardiologie	48	3	Klin. Chemie	33	3	Neurocentrum	75
Top 3: Gemiddelde impact factor score als 1e, 2e of laatste auteur:											
1	Cardiologie	8.9	1	Oogheelkunde	17.7	1	MDL	8.0	1	Klin. farmacie	9.8
2	Longziekten	5.8	2	Interne gnkd	11	2	KNO	5.4	2	Klin. chemie	9.6
3	Microbiologie	5.2	3	Intensive care	9.3	3	MKA chirurgie	5.4	3	Anesthesiologie	7.9

Overzicht aantal publicaties per vakgroep:

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Anesthesiologie	0	0	2	0	1	0	1	4	2	6
Cardiologie	21	25	28	39	31	40	27	40	-	-
Dermatologie	0	0	0	0	0	0	1	0	1	1
Gynaecologie	5	7	6	4	13	7	6	6	5	8
Heelkunde	13	21	31	26	30	20	39	23	43	67
Intensive Care	11	13	14	13	20	15	12	11	33	37
Interne Geneeskunde	16	20	17	8	11	24	14	27	35	39
Kindergeneeskunde	5	3	11	6	6	8	3	11	8	7
Klinische Chemie	2	6	7	5	5	7	4	8	12	12
Klinische Farmacie	4	6	8	10	3	8	13	7	14	12
Klinische Fysica	0	0	2	0	2	1	0	0	2	2
Klinische Psychologie	3	4	1	0	1	2	1	0	0	1
KNO	0	1	1	1	0	0	0	0	1	1
Longziekten	11	12	16	19	24	28	14	17	22	20
MDL	6	11	5	9	10	5	14	14	16	19
Medical School Twente	24	33	35	33	26	24	24	29	19	35
Microbiologie	7	2	2	4	3	1	2	0	1	12
MKA chirurgie	3	0	0	1	0	1	0	0	1	3
Neurochirurgie	*1*	*5*	*9*	*5*	*5*	*4*	*3*	-	-	-
Neurologie	*34*	*39*	*33*	*41*	*28*	*30*	*33*	-	-	-
Neurocentrum	-	-	-	-	-	-	-	29	52	52
Nucleaire Geneeskunde	0	0	2	0	0	0	0	0	0	0
Oogheelkunde	0	0	0	0	0	1	0	1	1	0
Orthopedie	0	4	7	5	4	2	5	3	13	16
Pathologie	1	5	8	4	9	3	4	0	0	1
Plastische Chirurgie	2	0	2	4	4	13	12	11	16	23
Psychiatrie	0	0	1	0	4	0	0	1	0	0
Raad van Bestuur	0	0	0	0	0	0	9	10	7	8
Radiologie	6	11	14	10	4	11	2	4	9	20
Radiotherapie	3	5	12	10	4	5	4	5	6	13
Reumatologie	32	20	23	15	7	15	17	11	10	19
Revalidatiegeneeskunde	7	8	6	0	0	1	0	0	0	0
Cardiologie	*21*	*25*	*28*	*39*	*31*	*40*	*27*	*40*	-	-
Thoraxchirurgie	*4*	*3*	*2*	*4*	*5*	*4*	*3*	*8*	-	-
Thoraxcentrum	-	-	-	-	-	-	-	-	47	47
Urologie	0	0	0	0	0	1	0	0	1	0
Waardegedreven zorg	-	-	-	-	-	-	-	-	4	1

Longgeneeskunde / Medical School Twente

Detection of lung cancer in exhaled breath
with electronic nose technology

Dissertation

to obtain
the degree of Doctor at the University of Twente,
on the authority of the Rector Magnificus,
Prof. Dr. Ir. A. Veldkamp,
on account of the decision of the Doctorate Board,
to be publicly defended
on Friday the 7th of October 2022 at 16.45 hours

by

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Samenvatting

Longkanker is wereldwijd de belangrijkste oorzaak van kanker-gerelateerde mortaliteit. Longkanker kan worden onderverdeeld in 2 typen: niet-kleincellig longcarcinoom (NSCLC) en kleincellig longcarcinoom (SCLC), welke respectievelijk circa 85% en 15% van de gevallen vormen. Daarnaast kan NSCLC verder worden onderverdeeld in meerdere subtypen, waarvan de twee meest voorkomende adenocarcinoom en plaveiselcelcarcinoom zijn, met elk hun eigen tumorkenmerken, behandelopties en prognose. De 5-jaars overleving van gelokaliseerd NSCLC ligt rond de 60%. Daarentegen ligt de 5-jaars overleving van gemetastaseerde ziekte slechts rond de 5%. In het geval van SCLC ligt de 5-jaars overleving van gelokaliseerde ziekte rond de 30% en bij gemetastaseerde ziekte is dit slechts 3%. Ondanks aanzienlijke verbeteringen in behandelopties de afgelopen jaren, zoals gerichte behandeling met tyrosinekinaseremmers (TKI's), immunotherapie, verbeteringen in chirurgische opties en gepersonaliseerde behandeling, reflecteert de hoge mortaliteit het feit dat de meeste mensen zich met reeds uitgebreide ziekte presenteren, waarbij curatie niet meer mogelijk is.

In de afgelopen decennia zijn er diverse niet-invasieve technologieën onderzocht als een potentieel diagnosticum voor longkanker. Dit betreft onder andere uitademingsanalyse gebaseerd op patroonherkenning door middel van een elektronische neus. Uitademingslucht bevat, naast anorganische componenten zoals waterdamp, koolstofdioxide, stikstof en koolstofmonoxide, ook duizenden vluchtige organische stoffen (VOC's) welke fysiologische en pathofysiologische processen in het lichaam reflecteren. In het geval van een ziekte verandert het metabolisme waardoor een andere samenstelling van VOC's wordt uitgeademd. Deze uitademingslucht kan worden geregistreerd door zeer gevoelige sensoren en vervolgens worden gemeten en geanalyseerd met verschillende kunstmatige intelligentie technieken. Dit type technologie komt overeen met de reuk bij mensen waarbij iemand eerst moet worden geleerd om een bepaalde geur te herkennen. In het geval van een elektronische neus wordt deze neus eerst geleerd en getraind welke 'geur' bij longkanker, of een andere ziekte past, waarna deze de volgende keer dezelfde geur kan matchen aan die specifieke ziekte. Om een dergelijk nieuw diagnosticum te implementeren, moet deze eerst getest en gevalideerd worden om te kunnen beoordelen of deze van voldoende additionele waarde is in de klinische praktijk.

In dit proefschrift hebben we de mogelijkheid van uitademingsanalyse om longkanker te diagnosticeren onderzocht, waarbij we een elektronische neus (Aeonose™) hebben getraind en gevalideerd om patiënten met longkanker te onderscheiden van personen zonder longkanker. Hoofdstukken 2 en 3 richten zich met name op methodologische kwesties rondom uitademingsanalyses gebaseerd op patroonherkenning met kunstmatige intelligentie technieken. Hoofdstukkers 4-6 laten resultaten zien van klinische studies waarbij de Aeonose™ is getraind en gevalideerd.

In hoofdstuk 2 hebben we in ons voorgestelde multicenter onderzoek uiteengezet hoe de Aeonose™ te trainen om longcarcinoom te diagnosticeren. Dit manuscript richt zich met name op de technologie achter de Aeonose™ en de statistische analyses gericht op kunstmatige intelligentie technieken en interne validatie technieken om personen te classificeren als het hebben van longkanker of niet. We laten zien hoe om te gaan met een grote hoeveelheid data om overfitting van een predictiemodel te voorkomen.

Zoals hierboven beschreven, nadat een predictiemodel ontwikkeld is op basis van training data, is het noodzakelijk om dit predictiemodel te valideren op nieuwe data om reproduceerbaarheid en generaliseerbaarheid van het model te beoordelen in een onafhankelijk groep mensen. Aangezien huidige diagnostische technieken zich snel ontwikkelen door uitermate innovatieve technologieën, duurt het soms te lang om personen voor een externe validatiestudie te includeren om goed de relevantie en efficiëntie van het ontwikkelde predictiemodel te kunnen beoordelen. In hoofdstuk 3

beschrijven we mogelijke studieopzet om tegelijkertijd een predictiemodel gebaseerd op kunstmatige intelligentie technieken te ontwikkelen en te valideren. Als voorbeeld gebruiken we onze training studie zoals gepubliceerd in 2018 als toepassing van deze voorgestelde studieopzet. Dit type studie design is voornamelijk geschikt in geval van een innovatieve, maar zeer relevante, diagnostische techniek die zich snel verder kan ontwikkelen, dan wel in geval van zeldzame ziektes waarbij inclusie van studiedeelnemers erg lang duurt.

Hoofdstukken 4-6 laten resultaten zien van klinische multicenter studies waarbij de Aeonose™ is getraind en gevalideerd. Het predictiemodel ontwikkeld op de training data is uitgebreid met klinische data om longkanker beter te kunnen diagnosticeren. In hoofdstuk 4 hebben we een exploratieve multicenter studie uitgevoerd om de Aeonose™ te trainen om mensen met en zonder niet-kleincellig longcarcinoom van elkaar te onderscheiden op basis van uitademingsanalyses. Er werden 290 mensen geïncludeerd (144 NSCLC patiënten en 146 controles), waarbij het ontwikkelde predictiemodel beide groepen kon onderscheiden met een sensitiviteit van 94%, een specificiteit van 33%, een negatief voorspellende waarde (NPV) van 86%, en een oppervlakte onder de receiver operating characteristic curve (AUC) van 0.76 (95% betrouwbaarheidsinterval (CI): 0.71-0.82). Aangezien longkanker wordt gekenmerkt door een hoge mortaliteit wanneer dit niet vroegtijdig wordt ontdekt, zijn de predictiemodellen gericht op een hoge negatief voorspellende waarde. Deze aangetoonde hoge negatief voorspellende waarde impliceert dat bij een groot deel van de personen verdacht voor longkanker voorkomen kan worden dat ze onnodig, mogelijk invasief vervolgonderzoek ondergaan. Naast evaluatie van het discriminerend vermogen van het predictiemodel tussen patiënten met en zonder niet-kleincellig longcarcinoom werden aanvullende sub analyses uitgevoerd gericht op de twee meest voorkomende subtypen van NSCLC: adenocarcinoom en plaveiselcelcarcinoom. Analyses gericht op plaveiselcelcarcinoom toonde een indrukwekkende hoge negatief voorspellende waarde van 93% met een AUC van 0.78, wat impliceert dat in geval van een absolute Aeonose™ waarde van lager dan -0.015, er met grote zekerheid en hoge klinische relevantie kan worden gesteld dat er geen sprake is van plaveiselcelcarcinoom. In geval van adenocarcinoom werd een iets lagere diagnostische nauwkeurigheid gevonden met een AUC van 0.73. Dit kan mogelijk verklaard worden door de heterogeniteit binnen adenocarcinomen. Ook werd in een kleine sub analyse gekeken naar verschillen in uitademingspatronen tussen SCLC- patiënten en personen zonder SCLC. Hierbij werden veelbelovende resultaten gevonden met een negatief voorspellende waarde van 97% en een AUC van 0.86 (95% CI: 0.78-0.95). Er moet echter worden benoemd dat deze sub analyses uitgevoerd zijn op datasets met een klein aantal inclusies. Daarnaast zijn alle analyses in de training studie uitgevoerd met een nog niet CE-gecertificeerd Aeonose™ apparaat en nog niet gevalideerd op onafhankelijke data.

In hoofdstuk 5 is de potentiële waarde onderzocht van het toevoegen van klinische variabelen aan het reeds ontwikkelde predictiemodel gebaseerd op de uitademingsdata van het training cohort zoals beschreven in hoofdstuk 4. Resultaten lieten zien dat de variabelen leeftijd, geslacht, rookstatus, aantal gerookte pakjaren, aanwezigheid van COPD en de absolute classificatiewaarde van de Aeonose™ geassocieerd waren met het hebben van longkanker. Vervolgens zijn 2 typen multivariabele analyses uitgevoerd om de toegevoegde waarde van de uitgebreide predictiemodellen te onderzoeken. Enerzijds is een multivariabele logistische regressieanalyse verricht met als input de absolute classificatiewaarde van de Aeonose™, zoals verkregen door de neurale netwerkanalyse, samen met de onafhankelijke klinische variabelen. Dit model toonde een aanzienlijke verbetering in diagnostische nauwkeurigheid om personen met en zonder NSCLC van elkaar te onderscheiden met een AUC van 0.86, een sensitiviteit van 96%, een specificiteit van 60%, en een NPV van 93%, vergeleken met het training model gebaseerd op enkel uitademingsdata (AUC 0.76). Vervolgens is een analyse verricht waarbij de vector van de uitademingsdata, die als input voor het neurale netwerk diende in de training studie, uitgebreid werd met de onafhankelijk geassocieerde klinische variabelen. Dit neurale netwerkmodel toonde eveneens een evidente verbetering in diagnostische nauwkeurigheid met een

AUC van 0.84, een sensitiviteit van 94%, een specificiteit van 49%, en een NPV van 90%. Beide uitgebreide modellen tonen niet alleen een verbetering van sensitiviteit en negatief voorspellende waarde, maar ook een toename van specificiteit wat betekent dat er minder personen onterecht geclassificeerd worden als het hebben van longkanker.

Aangezien de training studies, met en zonder het toevoegen van klinische variabelen, veelbelovende resultaten hebben getoond ten aanzien van het diagnosticeren van longkanker met de Aeonose™, is vervolgens een grote, multicenter, multinationale validatie studie verricht met meerdere Aeonose™ apparaten om reproduceerbaarheid en robuustheid van de verkregen resultaten te beoordelen. De resultaten van deze validatiestudie worden gepresenteerd in Hoofdstuk 6. In verband met continue verbeteringen in de elektronische neus technologie, zoals beschreven in Hoofdstuk 3, is er gebruik gemaakt van een tweede generatie, CE-gecertificeerd, Aeonose™ apparaat. Dit heeft als gevolg gehad dat de originele data van de training studie uit Hoofdstuk 4 niet konden worden gebruikt. In plaats daarvan zijn nieuwe proefpersonen geïncludeerd en is een split-sample studie design uitgevoerd om tegelijkertijd het nieuwe predictiemodel te ontwikkelen en te valideren. De training set bestond op 376 proefpersonen (160 NSCLC patiënten, 216 relevante controles) en de validatie set bestond uit 199 proefpersonen (79 NSCLC patiënten, 120 controles). In geval van een predictiemodel enkel op basis van uitademingsdata, werd een redelijke performance gezien om beide te groepen te onderscheiden met daarbij gelijke resultaten in de validatie set. Dit voorspellende model toonde, bij een afkapwaarde van 20% kans op longkanker, een sensitiviteit van 88%, een specificiteit van 48%, een positief voorspellende waarde van 52%, een negatief voorspellende waarde van 90% en een AUC van 0.79 (95% CI: 0.72-0.85) in de validatie set. Zoals ook gezien werd in Hoofdstuk 5, leidde het toevoegen van relevante klinische variabelen, die voorspellend zijn voor het hebben van longkanker, tot een aanzienlijke verbetering van diagnostische nauwkeurigheid van het predictiemodel. Uitademingsdata en klinische variabelen werden geanalyseerd middels een multivariabel logistisch regressiemodel op de training data, waarbij – bij een afkapwaarde van 16% kans op longkanker – een sensitiviteit van 95%, een specificiteit van 51% en een negatief voorspellende waarde van 94% werden gezien. Dit kwam overeen met een AUC van 0.87 (95% CI: 0.83-0.90). In geval van het toepassen van precies hetzelfde predictiemodel (gelijke formule met dezelfde B-coëfficiënten en handhaving van de afkapwaarde van 16% kans op longkanker) op de validatie set, zagen we sensitiviteit van 95%, een specificiteit van 49%, een positief voorspellende waarde van 54% en een negatief voorspellende waarde van 94% met een AUC van 0.86 (0.81-0.91). Dit zou betekenen, dat bij deze afkapwaarde van 16%, 63 van de 196 proefpersonen (32%) geclassificeerd zouden worden als het niet hebben van longkanker waarbij bij deze groep met grote zekerheid longkanker kan worden uitgesloten en onnodige invasieve onderzoeken kunnen worden voorkomen.

In hoofdstuk 7 plaatsen we de belangrijkste resultaten van de verrichte studies in een bredere context waarbij de relevantie en toekomstperspectieven worden besproken. Vervolgonderzoek is nodig om de waarde van uitademingsanalyse te beoordelen in longkanker screening programma's, maar ook als toepassing om behandelresponses te beoordelen en vroeg terugkeer van de ziekte op te sporen.

Heelkunde

Optimizing Outcome and Quality Of Life for
Mesenteric Ischemia Patients by Improving
Diagnostic and Treatment Strategies.

Dissertation

to obtain
the degree of Doctor at the University of Twente,
on the authority of the Rector Magnificus,
Prof. Dr. Ir. A. Veldkamp,
on account of the decision of the Doctorate Board,
to be publicly defended
on Friday 25 March 2022 at 12.45 hours

by

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Co-promotor:	dr. M.G.J. Brusse-Keizer

Samenvatting

Het doel van dit proefschrift was om een significante bijdrage te leveren aan de verbetering van de kwaliteit van leven (KvL) en de orgaan-sparende behandeling van patiënten met mesenteriale ischemie door meer inzicht te geven in de hedendaagse diagnostische en therapeutische ontwikkelingen. Meer bewustzijn creëren is de eerste stap in het loslaten van oude routines en overtuigingen.

Deel I Ontwikkelingen in de diagnostiek en de evolutie van de behandeling
Allereerst is het belangrijk om het diagnostisch proces te verbeteren, omdat diagnostische vertraging de belangrijkste factor is in de algehele morbiditeit, mortaliteit en maatschappelijke last van mesenteriale ischemie, voornamelijk voor patiënten met acute mesenteriale ischemie (AMI). In Deel I hebben we ons daarom gericht op de huidige status van diagnostische ontwikkelingen bij occlusieve AMI-patiënten. Patiënten en hun artsen hebben dringend behoefte aan een nauwkeurigere, minder invasieve, snelle en 24/7 beschikbare, kosteneffectieve diagnostische test. De gouden standaard is nu een 'hoge verdenking' gecombineerd met een 1-mm abdominale multislice meerfasen computer tomografische angiography (CTA)-scan.(1) Hoewel een CTA een sensitiviteit en specificiteit van 73-100% en 90-100% heeft voor het diagnosticeren van een acute occlusie van de arteria mesenterica superior (SMA), moet de mogelijke aanwezigheid van mesenteriale ischemie wel op voorhand herkend en erkend worden zodat de radiologische beelden correct kunnen en zullen worden beoordeeld.(1) Daarom, is er een toenemende belangstelling voor het mogelijke gebruik van biomarkers om diagnostische vertraging te verkorten. In **Hoofdstuk 2** hebben we een systematische review uitgevoerd om te bepalen of biomarkers enige diagnostische waarde hebben in het diagnostisch proces van AMI. We hebben 49 geschikte artikelen opgenomen die in totaal 60 verschillende biomarkers beschreven. We zagen echter een enorme heterogeniteit in de gebruikte in- en exclusiecriteria, patiënten populaties en controlegroepen, normaalwaarden en afkapwaarden, waardoor het vrijwel onmogelijk is om de uitkomsten met elkaar te vergelijken. Bovendien was de algehele methodologische kwaliteit van de artikelen laag. Voornamelijk vanwege het hoge aantal retrospectieve onderzoeken en het gebruik van een laparotomie als referentietest. Aangezien diagnostisering tijdens een laparotomie vaak betekent dat het al te laat is. Op basis van deze review concluderen we dat er tot nu toe geen definitieve beslissing kan worden genomen in het diagnostische proces van AMI-patiënten op basis van een biomarker of combinatie van biomarkers. Dit geldt ook voor leukocyten, lactaat en D-dimeer. De daadwerkelijke diagnose van AMI kan op dit moment alleen worden gesteld op basis van een hoge verdenking gevolgd door een multislice CTA.

Om echt orgaan-sparend te kunnen handelen en de KvL te verbeteren, moet natuurlijk het resultaat van de behandeling verbeteren. Daarom hebben we ons in Deel I vervolgens gefocust op de evolutie van behandelstrategieën en technieken die tegenwoordig beschikbaar zijn. Maar ook over de aanvullende en ondersteunende maatregelen die we onze patiënten kunnen bieden. Minimaal invasieve endovasculaire behandelingsopties zijn sinds de jaren 80 in opkomst en hebben als voordelen minder ziekenhuis gerelateerde mortaliteit en morbiditeit, kortere ziekenhuisopname en meer mogelijkheden voor hoog risicopatiënten, maar met een lagere primaire doorgankelijkheid en hogere percentages recidief klachten dan bij open chirurgische behandeling.(2, 3) In 2006 werd percutane mesenteriale arterie stenting (PMAS) de primaire behandelingsoptie voor patiënten met mesenteriale ischemie in het Medisch Spectrum Twente (MST). Om te zien of er nog plaats was voor open chirurgische mesenteriale arterie revascularisatie (OSMAR), evalueerden we de uitkomst van OSMAR bij patiënten met chronische mesenteriale ischemie (CMI) met stenosen van de arteria coeliaca (CA) of SMA die tussen 1997 en 2014 in het MST werden behandeld in **Hoofdstuk 3**. Patiënten werden ingedeeld in een groep van vóór 2006 of een groep na 2006. Technisch succes werd bij alle patiënten behaald, met meer klinisch falen in de historische groep, 30,4%, dan in de hedendaagse groep, 34,1%. De superieure primaire doorgankelijkheid van SMA-reconstructies in de

historische groep (1-, 3- en 5 jaar follow-up) was het enige significante verschil. Er waren trends van minder meertaks reconstructies, minder antegrade gelegen bypasses, verminderd klinisch succes maar verbeterde 30-dagen en lange termijn overleving na OSMAR. De meest voor de hand liggende verklaring hiervoor zou de uitgebreidere mesenteriale atherosclerose kunnen zijn en de ernst van de klinische situatie van de patiënt die OSMAR ondergaat in de "PMAS-first"-periode vanaf 2006. Deze studie toonde aan dat electieve OSMAR alleen mag worden gebruikt bij patiënten met een aanzienlijke fysiologische reserve, met ongunstige mesenteriale laesies, mislukte herhaalde PMAS of meerdere recidief stenoses of in-stent occlusies. Het versterkte ook onze overtuiging dat PMAS niet langer een "brug naar chirurgie" is voor CMI-patiënten, maar een sterke eerste keuzebehandeling, met een kanttekening van een "brug naar herhaalde PMAS".

In **Hoofdstuk 4** gingen we een stap verder om aan te tonen dat OSMAR niet eens tweede keus zou moeten zijn bij AMI-patiënten, omdat we een beter alternatief presenteerden waarbij de voordelen van open chirurgische en endovasculaire benaderingen gecombineerd worden, genaamd retrograde open mesenteriale stenting (ROMS). Het is een hybride techniek waarbij, via een kleine transversale bovenbuiklaparotomie, retrograad een stent in de SMA kan worden geplaatst met tevens de mogelijkheid om direct de darmvitaliteit te beoordelen. Tussen januari 2007 en september 2011 hebben we 15 opeenvolgende patiënten geïncludeerd die ROMS ondergingen voor AMI. Technisch succes werd behaald bij 14 patiënten. Twee patiënten hadden een ernstig ischemische dunne darm, waarvan één een gedeeltelijke darmresectie nodig had vanwege onomkeerbare transmurale ischemie. De 30-dagen mortaliteit was 20% en de primaire doorgankelijkheid was 92%. Tien patiënten ondergingen een ongeplande re-laparotomie, waarvan er één een resectie van een groot deel van de dunne darm nodig had. De 1-jaarsmortaliteit bleef 20%, met een primaire doorgankelijkheid van 83%. Primair ondersteunde doorgankelijkheid was 91% en de secundaire doorgankelijkheid was 100%. Klinisch succes na 30 dagen en 12 maanden was respectievelijk 73% en 67%. We waren niet de eersten die het geweldige resultaat van ROMS lieten zien, maar we toonden wel de grootste patiëntenpopulatie tot dan toe. En onze resultaten vormden onderdeel van de onderbouwing van Aanbeveling 26 in de ESVS 2017-richtlijn dat ROMS de tweede keus behandelingsoptie is voor AMI-patiënten.(1)

En om definitief ons statement te maken over de voordelen van PMAS voor AMI-patiënten, hebben we de huidige inzichten in behandelingsopties voor mesenteriale ischemie beschreven in **Hoofdstuk 5**. We hebben ook een kleine systematische review uitgevoerd van artikelen tussen september 2013 en juli 2016 waarin PMAS met OSMAR werd vergeleken. De uitkomsten vormen meerdere adviezen voor clinici om te integreren in hun dagelijkse praktijk. De meest essentiële boodschap bij het verbeteren van overleving, KvL en intestinale preservatie bij AMI is om "eerst te revasculariseren, alvorens te reserceren" en dat deze patiënten centra nodig hebben waar 24/7 specialistische zorg wordt geleverd, met ervaring in zowel open als endovasculaire revascularisatie.(4-8) Deze boodschap maakte de weg vrij voor Aanbeveling 10 in de ESVS 2017-richtlijn.(1) We toonden ook aan dat PMAS de eerste keus behandeling is voor AMI en CMI, met betere korte termijn resultaten, lagere mortaliteit en morbiditeit en lagere kosten.(2, 3, 5, 6, 9-35) En dat OSMAR alleen mag worden gebruikt bij laag risico patiënten met ongunstige mesenteriale laesies, mislukte herhaalde PMAS of ROMS of meerdere recidieven van in-stent stenose of occlusie.(4, 27) Bij aanhoudende ischemie of het onvermogen om te bepalen of aanvullende resectie nodig is, wordt een ‘second look’ laparotomie geadviseerd na 18-36 uur. Uitgestelde reconstructie van de darmcontinuïteit heeft de voorkeur boven het aanleggen van stoma's, vanwege de impact op morbiditeit en kwaliteit van leven.(5) Geleidelijke en strikt gecontroleerde herintroductie van voeding is cruciaal en alle patiënten moeten levenslang anticoagulantia krijgen.(36)

Deel II Leven na mesenteriale ischemie

Sinds 2017 zijn er 3 richtlijnen gepubliceerd die tot dezelfde conclusies zijn gekomen als dit proefschrift tot nu toe heeft beschreven. De grootste lacune in de huidige literatuur is onderzoek naar de impact van mesenteriale ischemie en de behandeling ervan op onze patiënten en hun kwaliteit van leven. Met andere woorden, genezen we onze patiënten daadwerkelijk en verbeteren we hun kwaliteit van leven? Dit werd voor zowel CMI- als niet- CMI-patiënten besproken in Deel II.

Het bestaan van mediane arquate ligament syndroom (MALS), ook wel bekend als het syndroom van Dunbar of het coeliacus arterie compressie syndroom (CACS), is al onderwerp van discussie sinds de eerste beschrijving ervan eind jaren vijftig, begin jaren zestig, wat leidde tot 'gelovigen' en 'niet-gelovigen'. Er zijn al veel discussies geweest over het al dan niet bestaan van deze ziekte en dus of patiënten behandeld moeten worden en of die behandeling zinvol is om de kwaliteit van leven te verbeteren, de ziektelast te verminderen en de sociale en financiële lasten voor de samenleving te verlagen. In **Hoofdstuk 6** hebben we een systematische review uitgevoerd naar de impact van chirurgische decompressie van het mediane arcuate ligament (MAL) op symptomen en kwaliteit van leven bij MALS-patiënten. De kwaliteit van de artikelen was erg laag met een grote heterogeniteit en de meeste artikelen presenteerden minder dan 10 patiënten. De behandeling van MALS verbeterde de kwaliteit van leven bij 68% van de patiënten. Dit ondersteund onze overtuiging van het bestaan van MALS en het mogelijke positieve effect van behandeling met endoscopische coeliacus arterie release, (e)CAR. Er is een grote behoefte aan een goede, prospectieve gerandomiseerde gecontroleerde studie (RCT) om echt te laten zien of MALS bestaat en of (e)CAR het antwoord is voor degenen die er last van hebben. Deze review toonde verder aan dat er geen redelijke ondersteuning is voor een neurogene oorsprong van MALS en dat er dus geen plaats is voor een plexusblokkade bij de behandeling van deze patiënten.

Namens de Dutch Mesenteric Ischemia Study Group (DMIS) hebben we in **Hoofdstuk 7** onze aanvraag voor het project 'Veelbelovende zorg' van het Zorginstituut voor deze dubbelblinde prospectieve ‘sham’ gecontroleerde RCT, de CARoSO-studie, gepresenteerd. Eventuele toekenning wordt verwacht in februari 2022, waarna we het onderzoeksprotocol kunnen publiceren en de studie kunnen starten. Zeventig patiënten zullen worden gerandomiseerd in een behandelingsgroep ((e)CAR) en een ‘sham’-groep om vast te stellen of het retroperitoneaal endovasculair klieven van de MAL de symptomen verlicht en de kwaliteit van leven verbetert (gemeten met de EQ-5D-5L) in een follow-up van twee jaar. De studie zal ofwel aantonen dat (e)CAR een (kosten)effectieve minimaal invasieve behandeling voor MALS is. Of het voorkomt dat in de toekomst patiënten een nutteloze interventie ondergaan. Als de effectiviteit van (e)CAR is bewezen, kunnen naar schatting alleen al in Nederland jaarlijks tot 490 patiënten met chronisch invaliderende buikklachten worden behandeld. Vanwege de relatief jonge leeftijd van 20-40 jaar van deze patiëntenpopulatie wordt een gemiddelde gezondheidswinst van 6,05 quality adjusted life years (QALY's)/patiënt verwacht. Daarnaast zou er tot € 4,3 miljoen maatschappelijke kosten per jaar kunnen worden bespaard, door een vermindering van het substantiële verlies aan productiviteit en zorgconsumptie veroorzaakt door MALS. Aangezien de noodzaak van het uitvoeren van deze studie is onderstreept door 2 recente internationale richtlijnen,(1, 37) zal de uitkomst van de CARoSO-studie worden vertaald in krachtige aanbevelingen in de komende updates van alle relevante (inter)nationale richtlijnen en, indien effectief, zal (e) CAR de standaardbehandeling voor MALS worden.

Er is dus weinig bekend over de impact die behandeling heeft op de kwaliteit van leven van MALS-patiënten, maar weten we iets over de impact die behandeling heeft op de kwaliteit van leven van CMI-patiënten in het algemeen? Dat hebben we onderzocht in **Hoofdstuk 8** en het bleek dat we de eersten waren die de impact van revascularisatie op de kwaliteit van leven van CMI-patiënten evalueerden. We vergeleken pre- en post-interventie KvL-gegevens gemeten met de EuroQol-5D door het minimale klinisch relevante verschil (MCID) te analyseren om te zien of er enige klinische relevantie was. Hiervoor hebben we de MCID van het prikkelbare darm syndroom (PDS) van 0,074

gebruikt, omdat er geen MCID is vastgesteld voor CMI. We toonden aan dat de mediane EQ-indexscore significant toenam van 0,70 naar 0,81 (P=0,02) met een gemiddeld verschil van 0,162, wat de MCID overschrijdt. Bovendien hadden patiënten een significante vermindering van symptomen in de domeinen dagelijkse activiteiten (34,4%) en pijn/ongemak (32,3%). Verder verbeterde de algehele huidige gezondheidstoestand uitgedrukt in de visueel analoge schaal (VAS) significant met 17% van 52 naar 69 (p=0,001). Deze bevindingen geven aan dat er een klinisch relevante verbetering van de kwaliteit van leven is na revascularisatie voor CMI-patiënten.

Het MST is een tertiair verwijzingscentrum voor patiënten met chronische abdominale klachten die verdacht worden van mesenteriale ischemie. Jaarlijks worden ongeveer 400 patiënten met mesenteriale ischemie behandeld, maar het aantal verwezen patiënten ligt hoger, omdat natuurlijk niet alle verwezen patiënten mesenteriale ischemie hebben. In **Hoofdstuk 9** voerden we een follow-up uit van patiënten die door het multidisciplinaire expertpanel geclassificeerd waren als klachten niet passend bij CMI, om te onderzoeken of het uitgebreide diagnostische werk, inclusief gedeelde besluitvorming, hun KvL beïnvloedde. Zes maanden na de beoordeling was de KvL klinisch significant verbeterd zonder dat de patiënten daadwerkelijk een behandeling hadden ondergaan. Dit effect verminderde echter na twee jaar en was na vier jaar volledig verdwenen. De korte termijn stijging van de kwaliteit van leven is mogelijk een gevolg van de aandacht en grondige evaluatie in het expertisecentrum voor mesenteriale ischemie. Hierdoor kan de verbetering van de kwaliteit van leven in de eerste maanden na een grondige analyse van de symptomen, zoals waargenomen in de huidige studie, optreden zonder een objectieve verandering in de onderliggende gezondheidstoestand en moet deze met voorzichtigheid worden geïnterpreteerd. Met andere woorden, dit geeft aan dat voor beoordeling van de KvL-verbetering van een interventie, een follow-up periode van zes maanden mogelijk te kort is.

Neurocentrum

Data, models and transitions
in computational neuroscience
Bottom-up and top-down approaches

Dissertation

to obtain
the degree of Doctor at the University of Twente,
on the authority of the Rector Magnificus,
Prof. Dr. Ir. A. Veldkamp,
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by

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Summary

This thesis is concerned with building and analyzing mathematical models in computational neuroscience using bottom-up and top-down approaches. Models are constructed using biophysical principles to understand the pathophysiology of cerebral ischemia at different spatial and temporal scales. Data-driven techniques in conjunction with machine learning are used to build compact parameter-dependent models from high-dimensional data. Finally, model maps are introduced to explain the generic unfolding of a newly observed bifurcation.

In Chapter 3, a comprehensive biophysical model of a glutamatergic synapse is developed, to identify key determinants of synaptic failure during energy deprivation. The model is based on fundamental biophysical principles, includes dynamics of the most relevant ions, i.e., Na+, K+, Ca2+, Cl− and glutamate, and is calibrated with experimental data. It confirms the critical role of the Na+/K+-ATPase in maintaining ion gradients, membrane potentials and cell volumes. The simulations demonstrate that the system exhibits two stable states, one physiological and one pathological. During energy deprivation, the physiological state may disappear, forcing a transit to the pathological state, which can be reverted when blocking voltage-gated Na+ and K+ channels. The model predicts that the transition to the pathological state is favoured if the extracellular space fraction is small. A reduction in the extracellular space volume fraction, as, e.g. observed with ageing, will thus promote the brain's susceptibility to ischemic damage. The work thus provides new insights into the brain's ability to recover from energy deprivation, with translational relevance for diagnosis and treatment of ischemic strokes.

In Chapter 4, the relationship between electroencephalogram (EEG phenomenology and cellular biophysical principles is studied using a model of interacting thalamic and cortical neural masses coupled with energy-dependent synaptic transmission. The model faithfully reproduces the characteristic EEG phenomenology during acute cerebral ischemia and shows that synaptic arrest occurs before cell swelling and irreversible neuronal depolarization. The early synaptic arrest is attributed to ion homeostatic failure due to dysfunctional Na+ /K+ -ATPase. Moreover, it is also shown that the excitatory input from relay cells to the cortex controls rhythmic behavior. In particular, low relay- interneuron interaction manifests in burst-like EEG behavior immediately prior to synaptic arrest. The model thus reconciles the implications of stroke on a cellular, synaptic and circuit level and provides a basis for exploring multi-scale therapeutic interventions.

In Chapter 5, deep learning autoencoders are introduced to discover coordinate transformations that capture the underlying parametric dependence of a dynamical system in terms of its canonical normal form, allowing for a simple representation of the parametric dependence and bifurcation structure. The autoencoder constrains the latent variable to adhere to a given normal form, thus allowing it to learn the appropriate coordinate transformation. The method is demonstrated on a number of example problems, showing that it can capture a diverse set of normal forms associated with Hopf, pitchfork, transcritical and/or saddle node bifurcations. This method shows how normal forms can be leveraged as canonical and universal building blocks in deep learning approaches for model discovery and reduced-order modeling.

Finally, in Chapter 6, a saddle to saddle-focus homoclinic transition when the stable leading eigenspace is 3-dimensional (called the 3DL-bifurcation) is analyzed. Here a pair of complex eigenvalues and a real eigenvalue exchange their position relative to the imaginary axis, giving rise to a 3-dimensional stable leading eigenspace at the critical parameter values. This transition is different from the standard Belyakov bifurcation, where a double real eigenvalue splits either into a pair of complex-conjugate eigenvalues or two distinct real eigenvalues. In the wild case, sets of codimension 1 and 2 bifurcation curves are obtained, along with points that asymptotically approach the 3DL-

bifurcation point and have a structure that differs from that of the standard Belyakov case. An example of this bifurcation is also provided in a perturbed Lorenz-Stenflo 4D ODE model.

Orthopedie

The ageing shoulder:
imaging, functional
assessment and arthroscopic
interventions

Proefschrift

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door

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Samenvatting

Als gevolg van zijn unieke anatomische en biomechanische aspecten laat het schoudergewricht een aantal typische verouderingspatronen zien. Omdat de westerse mens actief blijft tot op hogere leeftijd, stelt deze ook meer eisen aan de lichamelijke functionaliteit van het schoudergewricht. Rondom de behandeling van de oudere patiënt met schouderklachten zijn er nog altijd controverses op het gebied van beeldvorming, klinische testen en nieuwe behandeltechnieken. Deze thesis probeert meer helderheid te verschaffen op deze gebieden.

Deel 1: Het verouderende acromioclaviculaire gewricht
Deel 1 onderzoekt tekenen van het verouderen van het acromioclaviculaire gewricht (AC- gewricht). Het AC-gewricht is het gewricht tussen het sleutelbeen en het schouderblad en 1 van de 4 gewrichten die deel uitmaken van de schouder. Dit gewricht vertoont vaak slijtage (artrose), maar dat hoeft lang niet altijd klachten te geven. Om dit te onderzoeken, hebben we een groep patiënten met klinische klachten van het AC-gewricht vergeleken met een groep patiënten zonder klinische klachten van het AC-gewricht maar met andere schouderklachten, bijvoorbeeld het subacromiaal pijn syndroom. De MRI- scans van beide groepen hebben we vergeleken en we hebben meerdere kenmerken gevonden die voorspellend zijn voor klachten van het AC-gewricht. Botaangroei rond het AC-gewricht, vocht in de mergholte van het sleutelbeen, indeuking in de rotator- cuff-pees en een opbollend gewrichtskapsel worden elk afzonderlijk geassocieerd met klachten van AC-artrose. De resultaten van **Hoofdstuk 3** kunnen helpen bij klinische besluitvorming. De beschreven kenmerken zijn makkelijk te identificeren op een MRI en daarmee bruikbaar voor het diagnosticeren van symptomatische AC-artrose.

Deel 2: de verouderende rotator-cuff: functionele analyse en evaluatie van bestaande én nieuwe chirurgische technieken.
De rotator-cuff is een peesblad dat rond de schouder ligt, aan de binnenzijde vastzit aan 4 schouderspieren en aanhecht op de schouderkop aan de buitenzijde. Samen zorgen ze ervoor dat de schouderkop bij elke beweging centraal in de kom blijft. Hierdoor is er een ruime bewegelijkheid van de schouder. De rotator-cuff is 1 van de structuren van de schouder die regelmatig tekenen van slijtage laten zien bij het ouder worden. Tot wel 40 procent van de 60-plussers heeft scheuren in deze pezen. Dit hoeft alleen lang niet altijd klachten te geven. Bij patiënten met een gescheurde pees is het fascinerend om te zien dat ze hun arm kunnen bewegen, doordat andere spieren en pezen kunnen compenseren voor het functieverlies van de gescheurde pees. Deel 2 van dit proefschrift bestaat uit meerdere studies die de functie van de rotator-cuff analyseren en bestaande én nieuwe chirurgische technieken evalueren.

Hoofdstuk 4 analyseert de schouderbewegingen van patiënten met een rotator-cuff- scheur en vergelijkt deze gegevens met die van gezonde vrijwilligers, die even oud zijn en geen rotator-cuff-scheur hebben. Beide groepen hebben oefeningen uitgevoerd die gebaseerd zijn op dagelijkse activiteiten. Dit volgens de Functional Impairment Test- Hand and Neck/Shoulder/Arm (FIT-HaNSA). Dit moet gebeuren binnen een bepaalde tijd, waarbij de bewegingen met video en spieractiviteit met electromyografie worden gemeten. De groep patiënten met een rotator-cuff-scheur laat compenserende bewegingspatronen zien in vergelijking met de gezonde controlegroep van dezelfde leeftijd. De bicepsspier of tweehoofdige bovenarmspier en het achterste gedeelte van de deltaspier zijn opvallend actief bij de patiënten met een rotator-cuff-scheur. Bij de patiënten met een rotator-cuff-scheur werkt het achterste gedeelte van de deltaspier minder goed samen met de andere delen. Daarnaast werken de gedeelten van de rotator-cuff-spieren die nog intact zijn minder goed samen. Deze studie bevestigt dat het mogelijk kan helpen om de lange bicepspees te behandelen bij patiënten met klachten van een rotator-cuff-scheur.

Een rotator-cuff-scheur rechtstreeks hechten op het bot is niet altijd mogelijk. Dit is afhankelijk van meerdere factoren. Als de niet-operatieve behandeling niet effectief is en de scheur niet gehecht kan worden, wordt soms de lange bicepspees gekliefd tijdens een kijkoperatie: arthroscopie. Deze eenvoudige behandeling wordt vaak uitgevoerd als onderdeel van arthroscopische schouderoperaties. Het is alleen nog niet beschreven als solitaire ingreep. In **Hoofdstuk 5** presenteren we een groep van 64 patiënten van 65 jaar en ouder met een rotator-cuff-scheur, die zijn behandeld met deze techniek. Na de operatie zijn er minder pijnklachten en neemt de functie toe bij de meerderheid van de patiënten.

Er bestaan vele chirurgische technieken voor de behandeling van een massale rotator- cuff-scheur. **Hoofdstuk 6** beschrijft systematisch het gebruik van de lange bicepspees als transplantaat om als versterking te gebruiken bij het hechten van een gescheurde rotator-cuff-scheur aan de humeruskop. Uiteindelijk hebben we 8 onderzoeken gevonden en allen beschrijven een verschillende techniek voor het verkrijgen en daarna gebruiken van de lange bicepspees als versterking. De klinische resultaten van deze studies laten allen een significante verbetering zien van functie, afname van pijn en toename van bewegelijkheid. Deze studies vergelijken deze resultaten alleen niet met een controlegroep. Bij 82 procent van de patiënten van deze studies zijn de peesreconstructies intact bij MRI-onderzoek binnen 2 jaar. Dit laat zien dat een bicepspees gebruiken als versterking een goede optie kan zijn bij de operatieve behandeling van massale rotator-cuff-scheuren. We kunnen alleen geen definitieve aanbevelingen geven vanwege de wisselende kwaliteit van de studies.

Wegens de resultaten beschreven in Hoofdstuk 6, hebben we een nieuwe chirurgische techniek ontwikkeld. Hierbij gebruiken we de bicepspees voor reconstructie van de 'rotatorkabel', die **Hoofdstuk 7** beschrijft. Deze rotatorkabel is een natuurlijke versterking van de rotator-cuff en is vaak aangedaan in het geval van een massale rotator-cuff-scheur. Dit kan hersteld worden door de lange bicepspees te gebruiken als nieuwe rotatorkabel. In deze studie beschrijven we met foto's en een video deze nieuwe operatietechniek stap voor stap. In **Hoofdstuk 8** evalueren we de nieuwe techniek, waarbij we de lange bicepspees gebruiken als een transplantaat om de rotatorkabel te reconstrueren. Deze pilotstudie bestaat uit 4 patiënten van gemiddeld 64 jaar oud met een niet te repareren, massale rotator-cuff-scheur. Na 12 maanden lieten de meeste patiënten een significante verbetering zien op de klinische uitkomstscores, maar was er sprake van desintegratie van de gereconstrueerde kabel op de MRI. Deze nieuwe techniek laat vooralsnog geen voordelen zien boven beschreven technieken uit genoemde onderzoeken in Hoofdstuk 6. Nader onderzoek is gewenst.

Deel 3. Trends en tegenstrijdigheden bij de behandeling van de verouderende schouder
Deel 3 geeft een overzicht van trends in behandelingen van de verouderende schouder. Daarnaast diepen we een aantal controverses uit, zoals het wel of niet chirurgisch behandelen van een rotator-cuff-scheur. In 2014 heeft de Nederlandse Vereniging voor Orthopedie de richtlijn 'diagnose en behandeling van het subacromiaal pijnsyndroom (SAPS)' uitgebracht. SAPS is een symptomatische diagnose en een veel voorkomende oorzaak van pijn in de schouder bij volwassenen. Ieder jaar krijgen ongeveer 2 van de 100 volwassenen in Nederland last van deze schouderklachten. Bij patiënten met SAPS doet vooral het optillen van de arm pijn. Later is de schouder ook in rust pijnlijk. De pijn komt voort uit een veroudering, overbelasting of beschadiging van de pezen of spieren rondom het schoudergewricht. **Hoofdstuk 9** onderzoekt het effect van deze richtlijn op het handelen van orthopedisch chirurgen en huisartsen in Nederland. Door alle gedeclareerde diagnose-behandelcombinatie (DBCs) van de Nederlandse ziekenhuizen te analyseren, zijn er trends te zien in de operatieve en niet-operatieve behandeling van SAPS en rotator-cuff-scheuren. Van 2012 tot 2016 is de diagnose SAPS steeds minder vaak gesteld door orthopeden en is er een afname van 5% in operatieve behandelingen hiervan. Daarentegen worden er meer patiënten met een rotator-cuff-scheur gediagnosticeerd, maar over de jaren wordt steeds minder vaak een operatie uitgevoerd. Zoals de resultaten van deze studie laten zien, blijven er controverses bij de behandeling van

degeneratieve rotator-cuff-scheuren. Dit is ook te zien in de wetenschappelijk literatuur. Daarom geeft **Hoofdstuk 10** een overzicht van de huidige stand van de wetenschap als een pro et contra van rotator-cuff-operaties. Op dit onderwerp zijn vele studies verricht, waarbij nog geen eenduidig antwoord is over de meerwaarde van chirurgische behandeling en welke factoren van invloed zijn op genezing. Daarnaast is een alomvattende samenvatting gemaakt. De thesis eindigt met een algemene discussie die suggesties geeft over nog te verrichten onderzoek van schouderklachten bij ouderen.

Raad van Bestuur

Monitoring alcohol craving in daily life
Theories and methods for intensive longitudinal psycho-psychological studies

Dissertation

to obtain
the degree of Doctor at the University of Twente,
on the authority of the Rector Magnificus,
Prof. Dr. Ir. A. Veldkamp,
on account of the decision of the Doctorate Board,
to be publicly defended
on Friday 21 October 2022 at 14.45 hours

by

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Samenvatting

In deze thesis, wordt onderzocht in hoeverre het mogelijk is een solide wetenschappelijke basis te vinden voor een monitoring systeem bruikbaar is het dagelijks dat een individu in behandeling voor alcohol verslaving alert kan maken op situaties met een hoog risico voor alcohol trek en. De basis die wordt onderzocht betreft ambulante, fysiologische maten (zoals hartslag), regelmatige zelf rapportage van psychologische ervaringen (zoals negatieve gevoelens), en situaties in de context (zoals een gepland feestje). Aangezien dit een van eerste studies rond alcohol trek is die gebruikt maakt van longitudinale individuele casussen met herhaalde fysiologische metingen en ecological momentary assessment (EMA) in het dagelijks leven, zijn er verschillende voorbereidende studies gedaan voorafgaand aan het uiteindelijke monitoringsonderzoek.

In **hoofdstuk 2** worden actuele alcohol-trek modellen kritisch beoordeeld op basis van literatuuronderzoek om te bepalen wat het meest geschikte model van trek is voor theoretische onderbouwing en design keuzes voor onderzoek in het dagelijks leven. Achttien trek model zijn onderzocht door middel van een vijf-stappen strategie die een sneeuwbal techniek toepaste op een kernwoord extractie algoritme. Gebaseerd op dit literatuuronderzoek zijn meerdere besliscriteria geformuleerd, waarop de modellen vervolgens zijn geëvalueerd. Zes modellen werden voldoende onderbouwd door empirisch onderzoek om geschikt te zijn. De conclusies van deze zes modellen zijn vervolgens vertaald in drie relevante criteria: 1) negatief affect is een prominente trigger voor terugval in het dagelijks leven, 2) personen met alcoholverslaving hebben een hogere aandacht bias naar alcohol signalen, 3) stress leidt tot verhoogd risico op terugval. Gebaseerd op deze criteria, is het Affective Processing Model of Negative Reinforcement (Baker et al., 2004), wat vertaald kan worden als het affectieve processen model van negatieve bekrachtiging, beoordeeld als het meest geschikte model. Dit model stelt dat trek in alcohol voortkomt uit het ontsnappen aan de ongemakken van ontwenningsverschijnselen. Negatief affect wordt in dit model gezien als één van de ontwenningsverschijnselen. Volgens dit model, wordt deze trek versterkt door additionele stressoren. Dit model is, volgens dit literatuuronderzoek, het best passende model voor het beoogde monitoring systeem, met negatieve affect en stress als belangrijke triggers welke als parameters geïncludeerd worden in het monitoringsonderzoek van hoofdstuk 6.

In **hoofdstuk 3** worden de psychometrische kenmerken van de drinkwijzer (Alcohol Craving Situations and States (ACSS)) beoordeeld. De ACSS is een vragenlijst met 50 vragen en deze wordt gebruikt in online behandeling in Nederland, om personen met alcohol verslaging te laten bepalen hoeveel alcohol trek ze in diversie situaties en psychologische stemmingen ervaren op een schaal van 1 tot 3 (1= weinig/geen, 2= nogal, 3= heel erg). Van een grote heterogene populatie waren scores op de ACSS beschikbaar voor analyse (n=1439). Dit waren alle personen met problematisch alcohol gebruik of een alcohol verslaving, die op het moment van invullen deelnamen aan een online behandeling, maar nog in de voorbereidende fase voor gedragsverandering zaten. Aangezien de ACSS voortkomt uit de klinische praktijk in plaats van een theoretisch kader, werd de vragenlijst eerst vergeleken met de huidige modellen over alcohol trek in een inhoudelijke analyse. Daarna lieten we met een exploratieve en confirmatieve factor analyse zien dat de ACSS bestaat uit twee factoren met hoge interne consistentie: a) positieve sociale situaties en/of staat van zijn (PS-SS) en b) negatieve situaties en/of staat van zijn (N-SS). PS-SS vragen leidt tot een hoger zelf gerapporteerd gemiddelde voor alcohol trek dan N-SS. Dit wijst erop dat trek hoofdzakelijk ervaren wordt in een positieve context die voornamelijk sociaal van aard is. De gematigde sterke bijdrage van positieve sociale affectieve situaties die aanleiding geven tot trek, die gevonden wordt in deze steekproef suggereert dat deze factor mogelijk ondergewaardeerd wordt in bestaande modellen over trek (Skinner & Aubin, 2010). Daarom wordt PS-SS als variabele toegevoegd aan het model aangezien deze geen onderdeel zijn van het model van Baker et al (2004).

In **hoofdstuk 4** wordt er een uitgebreid validatie protocol ontwikkeld en beschreven voor fysiologische signalen, zoals electrodermale activiteit en cardiovasculaire activiteit, gemeten met draagbare technologie, zoals een polsband of slim horloge. Met dit protocol wordt de validiteit van E4 polsband, het apparaat dat gebruikt wordt in de monitoring studie geëvalueerd. De evaluatie van de validiteit gebeurt op 3 niveaus: 1) het signaalniveau met cross correlatie, 2) het parameterniveau met Bland Altman figuren, en 3) het gebeurtenis niveau waar de fysiologische veranderingen door externe stressors geëvalueerd worden in een specifiek daarvoor ontworpen statistisch figuur. Het advies is om op alle drie de niveaus onderzoek te doen en te rapporteren, aangezien een polsband mogelijk voor maar één van de drie levels valide is en dat dit niet direct betekent dat dit ook voor andere levels ook geldt. De gespecificeerde criteria uit het protocol maken het mogelijk om beslissingen te maken op ieder niveau. In eerdere validatie studies, waren deze besliscriteria vaak impliciet of zelf helemaal afwezig waardoor het moeilijk was onderbouwde beslissingen te maken of de studie te herhalen. Voor de E4, was het signaal niveau niet vergelijkbaar met de gouden standaard, al was dit de verwachting gegeven het verschil in techniek en plaatsing (aan de pols in plaats van de vingers) tussen de meeste polsbanden en de gouden standaard. Daarentegen bleek dat de E4 polsband wel valide gebruikt kan worden voor het verkrijgen van het huidgeleidingsniveau en de hartslag als parameters. Daarnaast kunnen huidgeleidingsresponses, gemiddelde huidgeleidingsniveau en hartslag gebruikt worden wanneer sterke ononderbroken stressoren onderzocht worden. Gegeven de groei in de aanwezigheid van dergelijke technieken in de wetenschappelijke, klinische en dagelijkse context, is een objectieve en goed onderbouwde beoordeling van validiteit belangrijk. Dit protocol geeft daar de mogelijkheid toe.

In **hoofdstuk 5** is het alcohol trek monitoring studie design getest door studenten met de E4 polsband en de EMA mobiele app. De E4 werd geëvalueerd op het nalevingspercentage, bruikbaarheid, comfort en mogelijke stigmatisering. Twee EMA methoden, namelijk op basis van een signaal en een interval ritme, werden vergeleken op de variabiliteit van de gerapporteerde trek, nalevering en de ervaarde belasting door het onderzoek. De resultaten, vergelijkbaar met ander onderzoek in gerelateerde domeinen (Csikszentmihalyi et al., 2013), zijn dat beide ritmes variabiliteit in trek registeren. Het bleek ook dat de ervaren belasting van het invullen voor meerdere vragenlijsten per dag hoog was, zeker voor het design met signalen op willekeurige momenten. Verder was voor beide EMA methodes het nalevingspercentage tussen laag en middelmatig, wat mogelijk tot problemen kan leiden. Blijkbaar moet er extra energie gestoken worden in de vervolgstudies om naleving te verhogen. Daarom is in de uiteindelijke studie het intervaldesign gebruikt in combinatie met micro-beloningen, zie hoofdstuk 6. Micro- beloningen zijn een bewezen methode om het nalevingspercentage te verhogen (Musthag et al., 2011). Participanten droegen de polsband soms tot vaak en vonden de bruikbaarheid van polsband goed. Ze rapporteerde wel diverse vragen over de polsband van mede studenten, vrienden en andere sociale contacten, wat zij als positief ervoeren. Echter is de vraag of personen met alcohol verslaving deze vragen als positief zouden ervaren, aangezien de polsband deel is van een onderzoek naar deze verslaving of een later mogelijk onderdeel van behandeling voor de verslaving. Daarom kregen participanten tijdens de uiteindelijke studie coping strategieën aangeboden om om te gaan met de vragen die ze zouden kunnen krijgen over de polsband en het onderzoek.

In **hoofdstuk 6**, wordt een ‘Naturalistic Settings Case-study’ beschreven wat gekenschetst kan worden als longitudinaal en intensief herhaald design met continue meeteenheden voor fysiologie, trek en misstappen met betrekking tot alcoholgebruik. Tien personen met alcohol verslaving werden voor 100 dagen gevolgd. De associatie tussen misstappen en trek verschilde enorm tussen individuen, variërend van zwak tot sterk geassocieerd. De meeste participanten hadden nooit een misstap zonder zelf-gerapporteerde trek, wat een duidelijke relatie tussen trek en misstappen laat zien. Echter, verschilde participanten sterk in hun fysieke reacties en psychologische ervaringen in de eerste maand van hun behandeling. Voor geen enkel individu in onze studie was er een unieke één-op-één vertaling van aan de ene kant fysiologische of psychologie triggers en aan de andere kant trek en misstappen of zelfs

terugval. De associatie tussen cardiovasculaire activiteit en verhoogde zelf-gerapporteerde trek was verwaarloosbaar tot zwak, echter wel met hoge specificiteit. Deze hoge specificiteit betekend dat er maar een paar trek momenten niet vergezeld werden door een bovengemiddelde hartslag. Dit zou impliceren dat er een relatie tussen cardiovasculaire activiteit en trek zou bestaan die niet exclusief is, maar waar meerdere andere psychologische invloeden ook nog mee spelen. De associatie tussen elektrodermale activiteit en trek was lager, dan die met cardiovasculaire activiteit, voor alle participanten op één na. Voor twee participanten kon deze relatie tussen fysiologie en trek nog verbeterd worden door het meenemen van de eerder beschreven context variabelen, zoals stress en sociale situaties, echter was de precisie hiervan erg laag.

De conclusie van dit proefschrift is dat het detecteren van en alarmeren voor risico situaties voor dreigende trek bij mensen in behandeling voor een alcohol verslaving op basis van fysiologie met een polsband en psychologische variabelen niet kan worden aanbevolen op basis van dit huidige onderzoek. Als een dergelijk systeem zou worden gebruikt dan zouden er veel te veel 'false alarms' worden gegeven. Er is wel toegevoegde waarde van het monitoren en vervolgens bespreken van de fysiologische metingen met een behandelaar om meer inzicht te krijgen in eigen trek en dagelijkse variaties in lichamelijke ervaringen.

Raad van Bestuur

The evolution of clinical care and
transmural medical pathways for
frail older adults with hip fractures

Proefschrift

ter verkrijging va
de graad van Doctor aan de Universiteit Twente
op gezag van de Rector Magnificus,
Prof. Dr. Ir. A. Veldkamp,
volgens het besluit van het College voor Promoties
in het openbaar te verdedigen
op vrijdag 15 juli 2022 om 16.45 uur

door

Wieke Stefanie Nijmeijer

geboren op 11 juni 1989
in Almelo, Nederland

Promotor:	Prof. Dr. Ir. M.M.R. Vollenbroek-Hutten
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Samenvatting

Een heupfractuur is een veelvoorkomend potentieel desastreus letsel voor ouderen. In 2025 zullen er wereldwijd jaarlijks 2.6 miljoen heupfracturen zijn. Een incidentie welke zal toenemen tot 6.3 miljoen heupfracturen in 2050, als gevolg van de toenemende levensverwachting.

Het doel van dit proefschrift is om de zorg voor ouderen met een heupfractuur te optimaliseren voorbijgaand aan de grenzen van de zorginstellingen: vanaf de opname in het ziekenhuis, tot aan de geriatrische revalidatie in de verpleeghuizen en de poliklinische follow-up. Om dit doel te realiseren focust het eerste deel (**Deel I**) van dit proefschrift zich op het identificeren van ouderen met een heupfractuur met een hoge kans op het ontwikkelen van een gecompliceerd beloop of overlijden. Hierdoor kan de behandeling mogelijk aangepast worden op de individuele behoeften van de patiënt in de hoop complicaties te voorkomen, of zo spoedig mogelijk te diagnosticeren zodat de ernst hiervan beperkt kan worden. In het tweede deel (**Deel II**) van dit proefschrift wordt het reeds bestaande intramurale orthogeriatrische zorgpad geëvalueerd en breiden we deze uit tot een digitaal transmuraal zorgpad, door de geriatrische revalidatie die plaatsvindt in de verpleeghuizen en de poliklinische follow-up mede te includeren.

DEEL I DE IDENTIFICATIE VAN HOOG-RISICO PATIENTEN

De toename van de levensverwachting maakt het waarschijnlijk dat het aantal heupfractuur patiënten met een leeftijd van 90 jaar of ouder (de zogenaamde 'nonagenarians') ook zal stijgen. Momenteel krijgt iedere heupfractuur patiënt met een leeftijd van 70 jaar of ouder dezelfde orthogeriatrische behandeling, waarbij er sprake is van dagelijkse betrokkenheid van de geriater. De resultaten gepresenteerd in **Hoofdstuk 2** van dit proefschrift laten zien dat heupfractuur patiënten met een leeftijd van 70 tot 89 jaar een significant lager risico hebben op het ontwikkelen van een anemie, hartfalen en over- lijden binnen 30 dagen en 1 jaar, in vergelijking met deze zogenaamde nonagenarians. Het risico op complicaties en mortaliteit nam toe met het ouder worden. Het lagere risico op complicaties en overlijden binnen patiënten met een leeftijd van 70 tot 89 jaar zou ervoor kunnen pleiten om een minder intensieve orthogeriatrische behandeling in te zetten bij deze relatief jongere patiëntenpopulatie. Dit zou kunnen geschieden door bijvoorbeeld enkel een geriatrische medebehandeling bij heupfractuur patiënten met een leeftijd van 70 tot 79 jaar in te zetten indien er sprake is van de aanwezigheid van bepaalde risicofactoren. Dit leidt tot het gerichter inzetten van geriaters. Het aanpassen van de intensiteit van de orthogeriatrische behandeling op basis van patiëntkarakteristieken kan bijdragen aan het optimaliseren van de efficiëntie in de zorg. Dit is belangrijk gezien de toenemende incidentie van heupfracturen gepaard gaande met hoge kosten en beperkte werkkracht.

Heupfractuur patiënten met een beperkte levensverwachting hebben mogelijk baat bij een niet-operatieve behandeling. Zij vermijden de stress van de chirurgische ingreep en de anesthesie en kunnen thuis blijven bij hun naasten in deze kwetsbare laatste levensfase. Maar wie zijn de heupfractuur patiënten met een beperkte levensverwachting bij wie een niet-operatieve behandeling overwogen zou moeten worden? De Almelo Hip Fracture Score (AHFS) (**Hoofdstuk 3**) identificeert patiënten met een hoog risico op vroegtijdig overlijden (gedefinieerd als binnen 30 dagen na de operatie). Deze risico- score includeert leeftijd, geslacht, het hemoglobinegehalte, cognitieve kwetsbaarheid, woonsituatie voor de fractuur, het aantal comorbiditeiten, de aanwezigheid van een maligniteit, de Parker Mobility Score en de American Society of Anaesthesiologists score (ASA score) als onafhankelijke voorspellers van mortaliteit. Het integreren van deze onafhankelijke risicofactoren in de zogenaamde 'AHFS' heeft geleid tot een risicoscore met een goede nauwkeurigheid.

Een beperking van de AHFS is dat de maximaal voorspelde kans op vroegtijdig overlijden met deze score 'slechts' 68.4% is. Een hogere maximaal voorspelde kans zou, samen met de klinische blik van de

arts, meer ondersteuning bieden in de klinische besluitvorming ten aanzien van een operatieve dan wel niet-operatieve behandeling. Theoretisch zou een minder scheve verhouding tussen overledenen en overlevers binnen de patiëntenpopulatie waarop het risicomodel gebouwd wordt de predictie kunnen verbeteren. Hiervoor is het wenselijk om een patiëntenpopulatie te gebruiken waarin het sterftecijfer hoger is, bijvoorbeeld de nonagenarians – zoals we hebben kunnen zien in Hoofdstuk 2. Zodoende is de Almelo Hip Fracture Score 90 ($AHFS^{90}$) ontwikkeld in **Hoofdstuk 4**, met als doel het voorspellen van vroegtijdig overlijden na een operatie binnen patiënten met een leeftijd van 90 jaar of ouder. Dit hoofdstuk laat zien dat binnen heupfractuur patiënten met een leeftijd van 90 jaar of ouder een hogere leeftijd, mannelijk geslacht, dementie, woonachtig zijn in een verpleeghuis, een hogere ASA score en een lager hemoglobinegehalte, onafhankelijke risicofactoren zijn voor vroegtijdig overlijden. De nauwkeurigheid van de $AHFS^{90}$ is vergelijkbaar met de AHFS na validatie. De maximaal voorspelde kans op vroegtijdig overlijden van 64.5% $AHFS^{90}$ was eveneens vergelijkbaar met de maximaal voorspelde kans op vroegtijdig overlijden van de AHFS, ondanks het hogere sterftecijfer in de studiepopulatie van de $AHFS^{90}$.

DEEL II DE EVOLUTIE VAN DE KLINISCHE ZORG: IN HET ZIEKENHUIS EN DAARBUITEN

De introductie van de orthogeriatrische behandeling voor ouderen met een heupfractuur in het Centrum voor Geriatrische Traumatologie (CvGT) in 2008 in Ziekenhuisgroep Twente (ZGT) heeft geleid tot een vermindering in complicaties en mortaliteit, gedurende de implementatiefase en de eerste jaren daarna. De lange termijn effecten van de implementatie van dit behandelmodel waren echter onbekend. **Hoofdstuk 5** laat zien dat de meeste uitkomsten van dit orthogeriatrische behandelmodel consistent zijn 10 jaar na implementatie, wanneer we naar de meeste complicaties en mortaliteit kijken. Veranderde complicatiecijfers werden gezien in het aantal postoperatieve anemieën, deliriums en urineweginfecties. De veranderde diagnostiek en behandelrichtlijnen beïnvloedden deze complicatiecijfers. Het blijven monitoren van klinische uitkomsten in de loop van de tijd wordt geadviseerd, met als doel het optimaliseren en behouden van de kwaliteit van zorg voor heupfractuur patiënten.

Na de orthogeriatrische behandeling in het CvGT wordt 47.8% van de heupfractuur patiënten ontslagen naar een revalidatieafdeling van één van de omliggende ver- pleeghuizen. In 2017 werd het transmurale 'Up&Go after hip fracture' project gestart, waarin Ziekenhuisgroep Twente en de omliggende verpleeghuizen Carintreggeland, TriviumMeulenbeltZorg en ZorgAccent de handen in een slaan om de kwaliteit van de transmurale zorg voor heupfractuur patiënten te verbeteren. Het ontwikkelen van een transmuraal zorgpad was een deel van dit project. **Hoofdstuk 6** is uniek in de gedetailleerde beschrijving van de ontwikkeling van een transmurale zorgpad voor heupfractuur patiënten dat het functioneel herstel na een operatie in verband met een heupfractuur monitort. Het zorgpad bestaand uit een ziekenhuisfase, een geriatrische revalidatiefase en een poliklinische follow-up fase (drie maanden na de operatie). De uitkomsten van het transmurale zorgpad laten zien dat gedurende de ziekenhuisfase patiënten achteruitgaan in functionaliteit en mobiliteitten gevolge van de fractuur en de operatie. Vervolgens neemt de functionaliteit en mobiliteit het meest toe gedurende de geriatrische revalidatiefase in het verpleeghuis. Tot slot is het herstel nog steeds gaande tijdens de poliklinische follow-up fase drie maanden na de operatie en waren op dat moment de meeste patiënten nog niet teruggekeerd op het oude functionele niveau van voor de fractuur. De resultaten van dit hoofdstuk laten zien dat het trans- murale zorgpad zorgt voor inzicht in de hersteltrajecten van heupfractuur patiënten, voorbijgaand aan de grenzen van zorginstellingen.

Ook binnen de Dutch Hip Fracture Audit (DHFA) - de nationale kwaliteitsregistratie welke als doel heeft het optimaliseren van de zorg voor heupfractuur patiënten - wordt het herstel van heupfractuur patiënten na drie maanden na de operatie gemeten. Het verzamelen van data rondom het herstel op dit moment blijkt echter een uitdaging te zijn. Het volledig registreren van gegevens betreffende het herstel na drie maanden na de heupfractuur operatie in de DHFA was landelijk slechts 36.2% in 2016

en 46.8% in 2020. Een oorzaak voor dit lage registratiepercentage is het feit dat veel heupfractuur patiënten hun poliklinische controle afspraak annuleren. Reden hiervoor zijn dat hun gezondheidstoestand het niet toelaat of, in geval van volledig herstel, niet nodig maakt om naar het ziekenhuis te komen. Dit heeft geleid tot het onderzoek gepresenteerd in **Hoofdstuk 7** waarin de bruikbaarheid en acceptatie van een applicatie voor op de mobiele telefoon werd getest. Deze applicatie had als doel informatie omtrent het herstel drie maanden na een heupfractuur operatie op afstand te verzamelen. Resultaten van dit onderzoek laten zien dat de implementatie van de applicatie niet-haalbaar was voor de dagelijkse praktijk, ondanks dat patiënten wel aangaven de intentie te hebben om de applicatie te gebruiken, ervaring te hebben met mobiele telefoons en er voldoende gunstige omstandigheden waren voor het gebruik van de mobiele telefoon. Redenen voor het falen van de applicatie waren technische problemen, een suboptimaal implementatieproces en cognitieve stoornissen bij de gebruikers. Toekomstig onderzoek zal moeten laten zien wat de bruikbaarheid van een dergelijke mobiele applicatie is, wan- neer de geïdentificeerde oorzaken van falen zijn ondervangen door het oplossen van technische problemen en het betrekken van deelnemers/naasten in de ontwikkeling van en de informatieverstrekking rondom de applicatie. Daarnaast zou het ambulant monitoren van herstel middels draagbare sensoren kunnen bijdragen in het verkrijgen van meer inzicht in het volledige herstel na een heupfractuur operatie.

CONCLUSIE

Dit proefschrift draagt bij aan de kennis en het begrip rondom individuele risico's na een heupfractuur operatie. Het identificeren van hoog-risicopatiënten in een vroegtijdig stadium zou kunnen bijdragen aan een proactieve behandeling op maat, gericht op de individuele behoeften van de patiënt. De hoeksteen van de besluitvorming rondom een operatieve of niet-operatieve behandeling is het multidisciplinair overleg, waarin de klinische beoordeling van de artsen en de individuele behandeldoelen van de patiënt gecombineerd en ter overweging genomen dienen te worden. Risicoscores zouden ondersteuning kunnen bieden in dit besluitvormingsproces. Dit proefschrift laat zien dat de huidige risicoscores voor het voorspellen van vroegtijdige mortaliteit accuraat zijn, maar dat er nog steeds ruimte is voor verbetering.

Daarnaast werden de uitkomsten van het intramurale orthogeriatrische zorgpad in dit proefschrift geëvalueerd en consistent bevonden. Dit zorgpad werd uitgebreid tot een transmuraal traject, waarin het verblijf op de geriatrische revalidatieafdelingen van de verpleeghuizen en poliklinische follow-up geïncludeerd werden. Op deze manier is het herstelproces van de patiënt voor zowel zorgprofessionals in het ziekenhuis als in de verpleeghuizen inzichtelijk, wat het mogelijk maakt om proactief de individuele behandeling aan te passen. De zorg voor patiënten met een heupfractuur gaat verder dan de grenzen van een zorginstelling en zou moeten worden benaderd vanuit het oogpunt van de gehele zorgketen.

Raad van Bestuur

Precautions following Total Hip Arthroplasty

Dissertation

to obtain
the degree of Doctor at the University of Twente
on the authority of the Rector Magnificus,
Prof. Dr. Ir. A. Veldkamp,
on account of the decision of the Doctorate Board
to be publicly defended
on Thursday 22 September 2022 at 16.45 hours

by

Anil Peters-Veluthamaningal

Born on the 26th of April, 1972
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Samenvatting

Het operatief vervangen van het heupgewricht door een totale heupprothese (THP) is een van de succesvolste en vaakst uitgevoerde electieve operaties. De posterolaterale benadering, is hiervoor de meest gebruikte chirurgische benadering zowel in Nederland als wereldwijd. Bij deze benadering is de veronderstelling dat er een groter risico op luxatie van de prothese is dan bij andere benaderingen. Leefregels na een THP worden van oudsher voorgeschreven voor een goede genezing van de weke delen en om een vroege luxatie (het uit de kom schieten) van de prothese te voorkomen. Leefregels kunnen worden onderverdeeld in bewegingsbeperkingen, het gebruik van hulpmiddelen en functionele beperkingen. De gehanteerde leefregels zijn gebaseerd op lang bestaande protocollen en kunnen belastend zijn voor de patiënt en het hervatten van activiteiten na een THP belemmeren. Er is steeds meer interesse in kennis over het gebruik van minder leefregels na een THP zonder dat het het risico op luxatie vergroot. Dit proefschrift heeft als doel bij te dragen de set postoperatieve leefregels na een posterolaterale THP te optimaliseren, door kennis te genereren over het huidige gebruik, de compliance (in hoeverre wordt het nageleefd), de ervaren belasting, en de effectiviteit.

In **Hoofdstuk 2** worden de resultaten gepresenteerd van een prospectief landelijk onderzoek naar het gebruik van leefregels na een THP in Nederland. De enquête is verstuurd naar alle orthopedisch chirurgen die lid zijn van de Nederlandse Orthopedische Vereniging (NOV) en werkzaam zijn op een van de orthopedische afdelingen in Nederland. De resultaten laten zien dat de meeste orthopedische afdelingen leefregels hanteren na een THP. Leefregels worden in verschillende mate gebruikt afhankelijk van de chirurgische benadering: anterieur (69%), anterolateraal (100%), straight-lateral (94%) en posterolateraal (93%). De duur dat deze leefregels worden voorgeschreven is over het algemeen 6 weken. Het percentage klinieken dat de leefregels voorschrijft de patiënten verplicht om op de rug te slapen is hoog voor de anterolaterale, straight-lateral en posterolaterale benaderingen (100%, 94% en 82%), en in minder bij de directe anterieure benadering (38%). De observatie dat patiënten in de dagelijkse praktijk klagen over de beperking die voorschrijft om op de rug te slapen na een THP, heeft geleid tot de opzet van een gerandomiseerde gecontroleerde studie (RCT), die wordt gepresenteerd in **Hoofdstuk 3**. Het unieke aan het ontwerp is dat alle patiënten hetzelfde implantaat hebben gekregen met een kopje van 32 mm; alle operaties werden uitgevoerd via een posterolaterale benadering; en slechts één specifieke leefregel, de instructie om op de rug te slapen, werd verwijderd. De controlegroep kreeg de standaardzorg met het de instructie op op de rug te slapen als een van de leefregels, terwijl de experimentele groep de standaardzorg kreeg waarbij de slaaphouding volledig vrij werd gelaten. De resultaten van deze studie worden gepresenteerd in Hoofdstukken 4 en 5. **Hoofdstuk 4** evalueert het aantal vroege luxaties van patiënten die al dan niet op hun rug moesten slapen in de eerste 8 weken na een THP via een posterolaterale benadering. De functionele uitkomsten van deze twee groepen werden gemeten met behulp van patient-reported outcome measures (PROMS). In totaal werden 456 patiënten geïncludeerd. De studie toonde aan dat het percentage vroege luxaties bij patiënten met een onbeperkte slaaphouding na een posterolaterale THP niet-inferieur (non-inferior) was aan het percentage vroege luxaties bij patiënten die geadviseerd worden om op de rug te slapen. Patiënten in beide groepen lieten na 8 weken postoperatief een significante verbetering in de PROMS zien ten opzichte van voor de operatie ($p < .001$). Voor de metingen werden de Hip Disability and Osteoarthritis Outcome Score (HOOS) en de EuroQoL 5-Dimension (EQ-5D) vragenlijsten gebruikt. Er werden geen statistisch significante of klinisch relevante verschillen in verbetering van de HOOS- en EQ-5D-scores gevonden tussen de twee groepen. In **Hoofdstuk 5** worden de resultaten gepresenteerd van onze RCT met betrekking tot belasting en compliance van leefregels. De compliance bij bewegingsbeperkingen is hoog. Daarentegen laten andere meer kliniek-specifieke beperkingen een minder duidelijk beeld zien met betrekking tot compliance. Over het algemeen lijkt de belasting van het beperken tot een bepaalde slaaphouding (63%) hoger dan die van bewegingsbeperkingen (29%). Bij de onbeperkte groep met

een vrije slaaphouding, was de belasting van een verplichte slaaphouding significant minder (P= 0,000). In **Hoofdstuk 6** worden de ontwerp behoeften voor een technisch hulpmiddel om patiënten te helpen bij hun individuele revalidatie en om postoperatieve leefregels op te volgen en te ondersteunen onderzocht. Het toekomstige technische apparaat werd het heupluxatie waarschuwingssysteem (HipDas) genoemd. Er werd een vragenlijst afgenomen bij patiënten die waren gepland voor een THP, een focusgroep werd gebruikt om de ontwerp behoeften te beoordelen. De bruikbaarheid van het ontwikkelde prototype werd getest en geëvalueerd door een hands-on sessie met patiënten na een THP-operatie. De resultaten laten zien dat 6 weken na de operatie, flexie van de heup > 90 graden, vooroverbuigen in een stoel en slapen op de rug de leefregels zijn met de laagste self-efficacy (het geloof in het eigen kunnen) voor de respondenten. THP-patiënten toonden zich ontvankelijk voor HipDas voor het verbeteren van hun self-efficacy niveau en beschouwden zichzelf als “matig” in staat om het te gebruiken. Het ontwikkelde prototype HipDas wordt als klinisch zeer relevant en bruikbaar beschouwd. In **Hoofdstuk 7** worden de belangrijkste bevindingen van onze studies en hun betekenis voor de klinische praktijk en toekomstperspectieven bediscussieerd. In het eerste deel wordt het beschikbare bewijs over leefregels besproken, en het bewijs dat is gegenereerd met betrekking tot het gebruik van een verminderde set aan leefregels. Het tweede deel reflecteert op de patiënt perspectieven met betrekking tot leefregels en een verschuiving van meer algemene leefregels naar een meer individuele begeleiding na een THP. Het derde deel bespreekt leefregels en hun relatie met nieuwe chirurgische benaderingen en op waardegedreven zorg. Concluderend maken leefregels deel uit van de huidige praktijk na een posterolaterale THP. Dit proefschrift laat zien dat er een grote verscheidenheid is aan voorgeschreven leefregels. De compliance met bewegingsbeperkingen groter is dan de compliance met functionele beperkingen. Dat de belasting van de leefregel die het verplicht om op de rug te slapen hoog is en dat deze leefregel effectief kan worden verwijderd zonder dat het het risico op luxatie vergroot. Het optimaliseren van de set postoperatieve leefregels na een posterolaterale THP creëert de mogelijkheid voor een meer gepersonaliseerde zorg.

Publicaties MST in 2022

Anesthesie

1. Preoperative anaemia and outcome after elective cardiac surgery: a Dutch national registry analysis
Hazen Y, Noordzij PG, Gerritse BM, Scohy TV, Houterman S, Bramer S, Berendsen RR, Bouwman RA, Eberl S, Haenen JSE, Hofland J, Ter Horst M, Kingma MF, Van Klarenbosch J, Klok T, De Korte MPJ, Van Der Maaten J, Spanjersberg AJ, Wietsma NE, van der Meer NJM, Rettig TCD, Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration: Speekenbrink RGH

Background: Previous studies have shown that preoperative anaemia in patients undergoing cardiac surgery is associated with adverse outcomes. However, most of these studies were retrospective, had a relatively small sample size, and were from a single centre. The aim of this study was to analyse the relationship between the severity of preoperative anaemia and short- and long-term mortality and morbidity in a large multicentre national cohort of patients undergoing cardiac surgery**.**
Methods: A nationwide, prospective, multicentre registry (Netherlands Heart Registration) of patients undergoing elective cardiac surgery between January 2013 and January 2019 was used for this observational study. Anaemia was defined according to the WHO criteria, and the main study endpoint was 120-day mortality. The association was investigated using multivariable logistic regression analysis**.**
Results: In total, 35 484 patients were studied, of whom 6802 (19.2%) were anaemic. Preoperative anaemia was associated with an increased risk of 120-day mortality (adjusted odds ratio [aOR] 1.7; 95% confidence interval [CI]: 1.4-1.9; P<0.001). The risk of 120-day mortality increased with anaemia severity (mild anaemia aOR 1.6; 95% CI: 1.3-1.9; P<0.001; and moderate-to-severe anaemia aOR 1.8; 95% CI: 1.4-2.4; P<0.001). Preoperative anaemia was associated with red blood cell transfusion and postoperative morbidity, the causes of which included renal failure, pneumonia, and myocardial infarction.
Conclusions: Preoperative anaemia was associated with mortality and morbidity after cardiac surgery. The risk of adverse outcomes increased with anaemia severity. Preoperative anaemia is a potential target for treatment to improve postoperative outcomes.

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Impact factor: 11.719 ; Q1

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2. Optimal postoperative pain management after VATS lung resection by thoracic epidural analgesia, continuous paravertebral block or single-shot intercostal nerve block (OPtriAL): study protocol of a three-arm multicentre randomised controlled trial
Spaans LN, Dijkgraaf MGW, Meijer P, Mourisse J, Bouwman RA, Verhagen A, van den Broek FJC, OPtriAL study group: van Duyn E, Potters JW

Background: Adequate pain control after video-assisted thoracoscopic surgery (VATS) for lung resection is important to improve postoperative mobilisation, recovery, and to prevent pulmonary complications. So far, no consensus exists on optimal postoperative pain management after VATS anatomic lung resection. Thoracic epidural analgesia (TEA) is the reference standard for postoperative pain management following VATS. Although the analgesic effect of TEA is clear, it is associated with patient immobilisation, bladder dysfunction and hypotension which may result in delayed recovery and longer hospitalisation. These disadvantages of TEA initiated the development of unilateral regional techniques for pain management. The most frequently used techniques are continuous paravertebral block (PVB) and single-shot intercostal nerve block (ICNB). We hypothesize

that using either PVB or ICNB is non-inferior to TEA regarding postoperative pain and superior regarding quality of recovery (QoR). Signifying faster postoperative mobilisation, reduced morbidity and shorter hospitalisation, these techniques may therefore reduce health care costs and improve patient satisfaction**.**
Methods: This multi-centre randomised study is a three-arm clinical trial comparing PVB, ICNB and TEA in a 1:1:1 ratio for pain (non-inferiority) and QoR (superiority) in 450 adult patients undergoing VATS anatomic lung resection. Patients will not be eligible for inclusion in case of contraindications for TEA, PVB or ICNB, chronic opioid use or if the lung surgeon estimates a high probability that the operation will be performed by thoracotomy.
Primary outcomes: (1) the proportion of pain scores >/= 4 as assessed by the numerical rating scale (NRS) measured during postoperative days (POD) 0-2; and (2) the QoR measured with the QoR-15 questionnaire on POD 1 and 2. Secondary outcome measures are cumulative use of opioids and analgesics, postoperative complications, hospitalisation, patient satisfaction and degree of mobility.
Discussion: The results of this trial will impact international guidelines with respect to perioperative care optimization after anatomic lung resection performed through VATS, and will determine the most cost-effective pain strategy and may reduce variability in postoperative pain management. Trial registration The trial is registered at the Netherlands Trial Register (NTR) on February 1st, 2021 (NL9243). The NTR is no longer available since June 24th, 2022 and therefore a revised protocol has been registered at ClinicalTrials.gov on August 5th, 2022 (NCT05491239).
Protocol version: version 3 (date 06-05-2022), ethical approval through an amendment (see ethical proof in the Study protocol proof).

Gepubliceerd: BMC Surg. 2022;22(1):330.
Impact factor: 2.030; Q3

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3. Nationwide Experience with EVAS Relining of Previous Open or Endovascular AAA Treatment in The Netherlands
Ketting S, Zoethout AC, Heyligers JMM, Wiersema AM, Yeung KK, Schurink GWH, Verhagen HJM, de Vries JPM, Reijnen M, Mees BME.

Objective: Relining of a previously placed surgical graft or endograft for an abdominal aortic aneurysm (AAA) is a reintervention to treat progression of disease or failure of the primary (endo)graft. Endovascular Aneurysm Sealing (EVAS) relining is a technique with potential advantages due to the absence of a bifurcation, the possibility for a unilateral approach, and sealing concept of the endobags. The purpose of this study was to describe the nationwide experience with EVAS relining of previous AAA repair in the Netherlands.
Methods: A retrospective analysis of all patients who underwent EVAS relining in 7 high volume vascular centres in the Netherlands between 2014 and 2019 was performed. Primary outcomes were technical and clinical success. Secondary outcomes were perioperative outcomes, complications and survival.
Results: Thirty-three patients underwent EVAS relining of open (n = 10) or endovascular (n = 23) repair. 26 were elective cases, 5 were urgent and 2 were acute (ruptured). Mean time between primary treatment and EVAS relining was 99 +/- 74 months. Indications after open repair were proximal progression of disease (n = 7) and graft defect (n = 3). Indications after EVAR were type IA (n = 10), type IB (n = 3), type IIIA (n = 4), type IIIB (n = 3) endoleak, and endotension (n = 3). 18 patients underwent regular EVAS, 4 unilateral EVAS and 11 chimney-EVAS. In-hospital mortality was 6% (both patients with rAAA). Technical success was achieved in 97%. Median follow-up after EVAS relining was 20 months (range 0-43). Freedom from reintervention at 1-year and 2-year were 83% and 61% and the estimated survival 79% and 71%, respectively. EVAS relining after open repair had a clinical

success of 90% at 1-year and of 70% at latest follow-up, while after EVAR clinical success rates were 70% and 52%, respectively.
Conclusion: EVAS relining of previous AAA repair is associated with high technical success, however with limited clinical success at median follow-up of 20 months. Clinical success was higher in patients with EVAS relining after open repair than after EVAR. In patients with failed AAA repair, EVAS relining should only be considered, when established techniques such as fenestrated repair or open conversion are not available or indicated.

Gepubliceerd: Ann Vasc Surg. 2022;84:250-64.
Impact factor: 1.607 ; Q4

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4. Bronchotracheal Compression Caused by Esophageal Impaction after Bilateral Lung Transplantation
Zoethout AC, Erasmus ME, Verschuuren E, Pillay J.

Gepubliceerd: Am J Respir Crit Care Med. 2022;205(7):842-3.
Impact factor: 24.700; Q1

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5. Systematic Review on the Mid-Term Outcomes of Elective Endovascular Aneurysm Sealing in Comparison to Endovascular Aneurysm Repair
Zoethout AC, Hochstenbach I, van der Laan MJ, de Vries JPM, Reijnen M, Zeebregts CJ.

Introduction: The Nellix endovascular aneurysm sealing (EVAS) system has been a topic of discussion. Early results were promising but did not deliver on the long-term and the device has been recalled from the market. This study compares literature for EVAS and conventional endovascular aneurysm repair (EVAR).
Methods: A systematic review and analysis was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. PubMed, Embase, and Cochrane Library were searched and identified the eligible studies. Proportion rates for the outcomes of interest were extracted. Subgroup analyses were performed for EVAS and EVAR.
Results: A total of 12 studies were included (EVAS n = 4, EVAR n = 8) including 10,255 patients (EVAS n = 784, EVAR n = 9441). The longest duration of follow-up was 3.4 years for EVAS and 5.0 years for EVAR studies. Throughout follow-up the overall all-cause mortality rates were 6% for EVAS and 13% for EVAR, and endoleak of any type was described in 10% of EVAS and 17% of EVAR patients. The migration rate >10 mm was 8% for EVAS and 0% for EVAR and aneurysm growth >5 mm was found in 11% of EVAS and 3% of EVAR cases. Total reintervention rate was 13% for EVAS and 7% for EVAR patients. For all analyzed outcome parameters heterogeneity was >50%.
Conclusion: There is a tendency toward lower mortality and overall endoleak rates for EVAS compared to EVAR but with a higher rate of migration, aneurysm growth, and reintervention. Despite lower overall endoleak rates there was a tendency toward less type II and more type I endoleaks after EVAS compared to EVAR. Substantial heterogeneity however limits robust statistical analyses, and is probably caused by significant instructions for use breach in EVAS-treated patients. We call for more high-quality and long-term follow-up studies on both EVAS and EVAR in order to confirm the trends found in this study.

Gepubliceerd: J Endovasc Ther. 2022;29(3):457-67.
Impact factor: 2.600; Q2

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6. An International, Multicenter Retrospective Observational Study to Assess Technical Success and Clinical Outcomes of Patients Treated with an Endovascular Aneurysm Sealing Device for Type III Endoleak

Zoethout AC, Ketting S, Zeebregts CJ, Apostolou D, Mees BME, Berg P, Beyrouti HE, De Vries JPM, Torella F, Migliari M, Silingardi R, Reijnen M.

Introduction: Type III endoleaks post-endovascular aortic aneurysm repair (EVAR) warrant treatment because they increase pressure within the aneurysm sac leading to increased rupture risk. The treatment may be difficult with regular endovascular devices. Endovascular aneurysm sealing (EVAS) might provide a treatment option for type III endoleaks, especially if located near the flow divider. This study aims to analyze clinical outcomes of EVAS for type III endoleaks after EVAR.
Methods: This is an international, retrospective, observational cohort study including data from 8 European institutions.
Results: A total of 20 patients were identified of which 80% had a type IIIb endoleak and the remainder (20%) a type IIIa endoleak. The median time between EVAR and EVAS was 49.5 months (28.5-89). Mean AAA diameter prior to EVAS revision was 76.6+/-19.9 mm. Technical success was achieved in 95%, 1 patient had technical failure due to a postoperative myocardial infarction resulting in death. Mean follow-up was 22.8+/-15.2 months. During follow-up 1 patient had a type Ia endoleak, and 1 patient had a new type IIIa endoleak at an untreated location. There were 5 patients with aneurysm growth. Five patients underwent AAA-related reinterventions indications being: growth with type II endoleak (n=3), type Ia endoleak (n=1), and iliac aneurysm (n=1). At 1-year follow-up, the freedom from clinical failure was 77.5%, freedom from all-cause mortality 94.7%, freedom from aneurysm-related mortality 95%, and freedom from aneurysm-related reinterventions 93.8%.
Conclusion: The EVAS relining can be safely performed to treat type III endoleaks with an acceptable technical success rate, a low 30-day mortality rate and no secondary ruptures at short-term follow-up. The relatively low clinical success rates, related to reinterventions and AAA enlargement, highlight the need for prolonged follow-up.

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Impact factor: 2.600; Q2

Totale impact factor: 13.749
Gemiddelde impact factor: 6.875

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 2.030
Gemiddelde impact factor: 2.030

Dermatologie

1. Noninfectious sternal wound inflammation after coronary artery bypass grafting in a patient with myelodysplastic syndrome: A no-touch approach
Ten Dam L, Ten Broeke M, Poot AM, Gilbers MD, Halfwerk FR.

Pyoderma gangrenosum (PG) is a rare, chronic inflammatory noninfectious dermatosis. It is associated with underlying systemic or hematological diseases such as myelodysplastic syndrome (MDS) and can be triggered after surgery. Recognition and diagnosis of PG can be difficult as it can mimic a wound infection. Misdiagnosis could lead to invasive procedures which worsen the disease and have possible disastrous aftermath. A 74-year-old male with a history of MDS presents with an atypical sternal wound inflammation. Diagnosis confirmed PG after skin biopsy. No surgical or invasive procedures were performed and the patient was treated on an outpatient basis with prednisolone, clobetasol cream, and cyclosporine. This case shows the importance of a rapid diagnosis of the disease. Awareness is required for the diagnosis of PG in a wound with pronounced livid borders, without improvement after antibiotic treatment or worsening after debridement. Rapid diagnosis and treatment reduce high healthcare costs, morbidity, and mortality.

Gepubliceerd: J Card Surg. 2022;37(8):2419-22.
Impact factor: 1.778 ; Q3

Totale impact factor: 1.778
Gemiddelde impact factor: 1.778

Aantal artikelen 1e, 2e of laatste auteur: 0
Totale impact factor: 0
Gemiddelde impact factor: 0

Gynaecologie

1. Planned delivery or expectant management in preeclampsia: an individual participant data meta-analysis
Beardmore-Gray A, Seed PT, Fleminger J, Zwertbroek E, Bernardes T, Mol BW, Battersby C, Koopmans C, Broekhuijsen K, Boers K, Owens MY, Thornton J, Green M, Shennan AH, Groen H, Chappell LC.

Objective: Pregnancy hypertension is a leading cause of maternal and perinatal mortality and morbidity. Between 34(+0) and 36(+6) weeks gestation, it is uncertain whether planned delivery could reduce maternal complications without serious neonatal consequences. In this individual participant data meta-analysis, we aimed to compare planned delivery to expectant management, focusing specifically on women with preeclampsia. DATA SOURCES: We performed an electronic database search using a prespecified search strategy, including trials published between January 1, 2000 and December 18, 2021. We sought individual participant-level data from all eligible trials.
Study eligibility criteria: We included women with singleton or multifetal pregnancies with preeclampsia from 34 weeks gestation onward**.**
Methods: The primary maternal outcome was a composite of maternal mortality or morbidity. The primary perinatal outcome was a composite of perinatal mortality or morbidity. We analyzed all the available data for each prespecified outcome on an intention-to-treat basis. For primary individual patient data analyses, we used a 1-stage fixed effects model**.**
Results: We included 1790 participants from 6 trials in our analysis. Planned delivery from 34 weeks gestation onward significantly reduced the risk of maternal morbidity (2.6% vs 4.4%; adjusted risk ratio, 0.59; 95% confidence interval, 0.36-0.98) compared with expectant management. The primary composite perinatal outcome was increased by planned delivery (20.9% vs 17.1%; adjusted risk ratio, 1.22; 95% confidence interval, 1.01-1.47), driven by short-term neonatal respiratory morbidity. However, infants in the expectant management group were more likely to be born small for gestational age (7.8% vs 10.6%; risk ratio, 0.74; 95% confidence interval, 0.55-0.99)**.**
Conclusion: Planned early delivery in women with late preterm preeclampsia provides clear maternal benefits and may reduce the risk of the infant being born small for gestational age, with a possible increase in short-term neonatal respiratory morbidity. The potential benefits and risks of prolonging a pregnancy complicated by preeclampsia should be discussed with women as part of a shared decision-making process.

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Impact factor: 10.693 ; Q1

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2. Patient-Reported Outcome and Experience Measures in Perinatal Care to Guide Clinical Practice: Prospective Observational Study
Depla AL, Lamain-de Ruiter M, Laureij LT, Ernst-Smelt HE, Hazelzet JA, Franx A, Bekker MN, BUZZ project team: Baalman JH.

Background: The International Consortium for Health Outcomes Measurement has published a set of patient-centered outcome measures for pregnancy and childbirth (PCB set), including patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs). To establish value-based pregnancy and childbirth care, the PCB set was implemented in the Netherlands, using the outcomes on the patient level for shared decision-making and on an aggregated level for quality improvement.
Objective: This study aims to report first outcomes, experiences, and practice insights of implementing the PCB set in clinical practice**.**

Methods: In total, 7 obstetric care networks across the Netherlands, each consisting of 1 or 2 hospitals and multiple community midwifery practices (ranging in number from 2 to 18), implemented the PROM and PREM domains of the PCB set as part of clinical routine. This observational study included all women participating in the clinical project. PROMs and PREMs were assessed with questionnaires at 5 time points: 2 during pregnancy and 3 post partum. Clinical threshold values (alerts) supported care professionals interpreting the answers, indicating possibly alarming outcomes per domain. Data collection took place from February 2020 to September 2021. Data analysis included missing (pattern) analysis, sum scores, alert rates, and sensitivity analysis**.**
Results: In total, 1923 questionnaires were collected across the 5 time points: 816 (42.43%) at T1 (first trimester), 793 (41.23%) at T2 (early third trimester), 125 (6.5%) at T3 (maternity week), 170 (8.84%) at T4 (6 weeks post partum), and 19 (1%) at T5 (6 months post partum). Of these, 84% (1615/1923) were filled out completely. Missing items per domain ranged from 0% to 13%, with the highest missing rates for depression, pain with intercourse, and experience with pain relief at birth. No notable missing patterns were found. For the PROM domains, relatively high alert rates were found both in pregnancy and post partum for incontinence (469/1798, 26.08%), pain with intercourse (229/1005, 22.79%), breastfeeding self-efficacy (175/765, 22.88%), and mother-child bonding (122/288, 42.36%). Regarding the PREM domains, the highest alert rates were found for birth experience (37/170, 21.76%), shared decision-making (101/982, 10.29%), and discussing pain relief ante partum (310/793, 39.09%). Some domains showed very little clinical variation; for example, role of the mother and satisfaction with care.
Conclusions: The PCB set is a useful tool to assess patient-reported outcomes and experiences that need to be addressed over the whole course of pregnancy and childbirth. Our results provide opportunities to improve and personalize perinatal care. Furthermore, we could propose several recommendations regarding methods and timeline of measurements based on our findings. This study supports the implementation of the PCB set in clinical practice, thereby advancing the transformation toward patient-centered, value-based health care for pregnancy and childbirth.

Gepubliceerd: J Med Internet Res. 2022;24(7):e37725.
Impact factor: 7.077 ; Q1

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3. STop OVarian CAncer (STOPOVCA) young: Protocol for a multicenter follow-up study to determine the long-term effects of opportunistic salpingectomy on age at menopause
Gelderblom ME, IntHout J, Hermens R, Coppus S, Ebisch I, van Ginkel AA, van de Laar R, de Lange N, Maassen M, Pijlman B, Smedts HPM, Vos MC, Beerendonk CCM, de Hullu JA, Piek JMJ.

Background: Opportunistic salpingectomy comprises additional bilateral salpingectomy during abdominal surgery as a prophylactic method to reduce the risk of ovarian cancer. However, opportunistic salpingectomy may potentially damage (micro)blood circulation to the ovaries, resulting in earlier onset of menopause.
Primary objective: To evaluate the long-term effects of opportunistic salpingectomy on the onset of menopause in women who underwent sterilization through salpingectomy compared with a control group who underwent sterilization by tubal ligation or no surgery at all.
Study hypothesis: Opportunistic salpingectomy does not lower the mean age at onset of menopause.
Trial design: In a multicenter observational noninferiority study, we will prospectively compare the age at menopause of women initially aged 35-45 who underwent sterilization through opportunistic salpingectomy with a similarly aged control group who underwent sterilization by tubal ligation or no sterilization. Participants will be asked to complete an annual questionnaire on onset of menopause to eventually determine whether there is more than a one-year decrease in mean age at onset of

menopause in the opportunistic salpingectomy group. Follow-up will last until determination of menopause, with a maximum of 15 years.
Major inclusion/exclusion criteria: Inclusion criteria: pre-menopausal; age between 35 and 45; intact ovaries. Exclusion criteria: post-menopausal; previous bilateral salpingectomy or oophorectomy; previous hysterectomy; abnormal karyotype; previous or current chemotherapy or pelvic radiation.
Primary endpoint(s): Determination of age of menopause measured by annual questionnaire.
Sample size: 1200 (400 intervention group; 800 control group).
Estimated dates for completing accrual and presenting results: It is estimated that recruitment will be completed by 2023 and results will be published by 2039.
Gov identifier: NCT04757922
Protocol version: : Version 1, February 2021.

Gepubliceerd: Maturitas. 2022;159:62-8.
Impact factor: 5.110 ; Q1

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4. Incomplete surgical staging in clinical early-stage ovarian cancer: guidelines versus daily practice
Laven P, Beltman JJ, Bense JE, van der Aa MA, Van Gorp T, Vos MC, Boll D, Arts H, Reesink N, Trimbos JB, Kruitwagen R.

Background: Incomplete surgical staging of patients with early-stage epithelial ovarian cancer (EOC) has been reported in up to 98% of cases, when based on the International Federation of Obstetrics and Gynecology (FIGO) staging procedure. The aim of the present retrospective study was to clarify the reasons for incomplete staging**.**
Methods: The PRISMA (Prevention Recovery Information System for Monitoring and Analysis) technique was used to evaluate cases with FIGO I-IIa EOC based on incomplete staging from five gynecologic oncologic center hospitals in the Netherlands in the period 2010-2014**.**
Results: Fifty cases with an incomplete surgical staging of EOC according to national guidelines were included. The most common reasons for incomplete staging were insufficient random biopsies of the peritoneum (n = 34, 68%), and less than ten lymph nodes being resected and/or found at pathology (n = 16, 32%). The most mentioned reason for not performing biopsies was, besides forgetting to do so, believing that after careful inspection and palpation, taking biopsies is irrelevant and/or already are being taken while performing a hysterectomy (peritoneum of cul-de-sac, bladder). The value of contralateral pelvic lymph node dissection in case of a unilateral ovarian malignancy was also doubted, influencing the number of lymph nodes resected.
Conclusions: The most important reasons for incomplete staging in EOC are, besides omitting elements by accident, questioning the importance of obligatory elements of the staging procedure. A structured list of staging steps during surgery and more evidence-based consensus concerning these obligatory elements might increase the number of complete staging procedures in EOC.

Gepubliceerd: Surg Open Sci. 2022;7:6-11.
Impact factor: 0 ; Q NVT

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5. Adjuvant Use of PlasmaJet Device During Cytoreductive Surgery for Advanced-Stage Ovarian Cancer: Results of the PlaComOv-study, a Randomized Controlled Trial in The Netherlands
Nieuwenhuyzen-de Boer GM, Hofhuis W, Reesink-Peters N, Willemsen S, Boere IA, Schoots IG, Piek JMJ, Hofman LN, Beltman JJ, van Driel WJ, Werner HMJ, Baalbergen A, van Haaften-de Jong A, Dorman M, Haans L, Nedelcu I, Ewing-Graham PC, van Beekhuizen HJ.

Objective: Standard surgical treatment of advanced-stage ovarian carcinoma with electrosurgery cannot always result in complete cytoreductive surgery (CRS), especially when many small metastases are found on the mesentery and intestinal surface. We investigated whether adjuvant use of a neutral argon plasma device can help increase the complete cytoreduction rate.
Patients and Methods: 327 patients with FIGO stage IIIB-IV epithelial ovarian cancer (EOC) who underwent primary or interval CRS were randomized to either surgery with neutral argon plasma (PlasmaJet) (intervention) or without PlasmaJet (control group). The primary outcome was the percentage of complete CRS. The secondary outcomes were duration of surgery, blood loss, number of bowel resections and colostomies, hospitalization, 30-day morbidity, and quality of life (QoL)**.**
Results: Complete CRS was achieved in 119 patients (75.8%) in the intervention group and 115 patients (67.6%) in the control group (risk difference (RD) 8.2%, 95% confidence interval (CI) -0.021 to 0.181; P = 0.131). In a per-protocol analysis excluding patients with unresectable disease, complete CRS was obtained in 85.6% in the intervention group and 71.5% in the control group (RD 14.1%, 95% CI 0.042 to 0.235; P = 0.005). Patient-reported QoL at 6 months after surgery differed between groups in favor of PlasmaJet surgery (95% CI 0.455-8.350; P = 0.029). Other secondary outcomes did not differ significantly.
Conclusions: Adjuvant use of PlasmaJet during CRS for advanced-stage ovarian cancer resulted in a significantly higher proportion of complete CRS in patients with resectable disease and higher QoL at 6 months after surgery. (Funded by ZonMw, Trial Register NL62035.078.17.)
Trial registration: Approved by the Medical Ethics Review Board of the Erasmus University Medical Center Rotterdam, the Netherlands, NL62035.078.17 on 20-11-2017. Recruitment started on 30-1-2018.

Gepubliceerd: Ann Surg Oncol. 2022;29(8):4833-43.
Impact factor: 4.339 ; Q1

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6. Recurrence and survival after laparoscopy versus laparotomy without lymphadenectomy in early-stage endometrial cancer: Long-term outcomes of a randomised trial
Reijntjes B, van Suijlichem M, Woolderink JM, Bongers MY, Reesink-Peters N, Paulsen L, van der Hurk PJ, Kraayenbrink AA, Apperloo MJA, Slangen B, Schukken T, Tummers F, van Kesteren PJM, Huirne JAF, Boskamp D, Lunter G, de Bock GH, Mourits MJE.

Background: Laparoscopic hysterectomy is accepted worldwide as the standard treatment option for early-stage endometrial cancer. However, there are limited data on long-term survival, particularly when no lymphadenectomy is performed. We compared the survival outcomes of total laparoscopic hysterectomy (TLH) and total abdominal hysterectomy (TAH), both without lymphadenectomy, for early-stage endometrial cancer up to 5 years postoperatively**.**
Methods: Follow-up of a multi-centre, randomised controlled trial comparing TLH and TAH, without routine lymphadenectomy, for women with stage I endometrial cancer. Enrolment was between 2007 and 2009 by 2:1 randomisation to TLH or TAH. Outcomes were disease-free survival (DFS), overall survival (OS), disease-specific survival (DSS), and primary site of recurrence. Multivariable Cox regression analyses were adjusted for age, stage, grade, and radiotherapy with adjusted hazard ratios (aHR) and 95% confidence intervals (95%CI) reported. To test for significance, non-inferiority margins were defined**.**
Results: In total, 279 women underwent a surgical procedure, of whom 263 (94%) had follow-up data. For the TLH (n = 175) and TAH (n = 88) groups, DFS (90.3% vs 84.1%; aHR[recurrence], 0.69; 95%CI, 0.31-1.52), OS (89.2% vs 82.8%; aHR[death], 0.60; 95%CI, 0.30-1.19), and DSS (95.0% vs 89.8%; aHR[death], 0.62; 95%CI, 0.23-1.70) were reported at 5 years. At a 10% significance level, and with a non-inferiority margin of 0.20, the null hypothesis of inferiority was rejected for all three

outcomes. There were no port-site or wound metastases, and local recurrence rates were comparable**.**
Conclusion: Disease recurrence and 5-year survival rates were comparable between the TLH and TAH groups and comparable to studies with lymphadenectomy, supporting the widespread use of TLH without lymphadenectomy as the primary treatment for early-stage, low-grade endometrial cancer.

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Impact factor: 5.304 ; Q1

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7. Insights into ovarian response with a fixed low dose FSH stimulation in an IUI programme: the PRORAILS study
Rutten A, van Ballegooijen H, Broekmans F, Cohlen B, PRORAILS study group: Verberg MFG.

Study question: Are patients' characteristics, such as anti-Müllerian hormone (AMH) and BMI, reliable factors to predict ovarian response in couples with unexplained subfertility undergoing IUI with ovarian hyperstimulation (IUI-OH)?
Summary answer: We observed no solid relationship between serum AMH and ovarian response.
What is known already: Ovarian stimulation during IUI treatment could lead to a higher chance of pregnancy, but also a higher incidence of multiple pregnancies, unless strict cancellation criteria are being used. Several factors could influence the result of the stimulation, such as age, BMI and hormonal status of the female. In IVF treatment, AMH has shown to be a useful predictor of ovarian stimulation to optimize the outcome; however, in a milder stimulation protocol, such as IUI, this has not been investigated.
Study design, size, duration: We performed a prospective cohort study and evaluated the first IUI stimulation cycle of 492 patients. The study was conducted between 2012 and 2017. Follow-up ended if patients were not pregnant after the first cycle. If pregnancy did occur, follow-up lasted until delivery.
Participants/materials, setting, methods: PRORAILS is a large multicentre nationwide cohort study executed in the Netherlands. Eligible women aged 18-43 years who were diagnosed with unexplained subfertility or mild male subfertility according to the Dutch guideline, with a regular indication for IUI-OH, were asked to participate. Ovarian response was assessed using a transvaginal ultrasound 5-7 days after initiation of the stimulation and was repeated according to the size of the leading follicles. Ovarian response was defined as optimal or suboptimal based on the total number of dominant follicles >15 mm. A successful stimulation was defined as the presence of two to three follicles >15 mm on the day of hCG administration. Serum AMH (µg/l) was measured by ELISA, and samples were taken on day 2, 3 or 4 of the menstrual cycle. Poisson regression was used to estimate the risk of a suboptimal ovarian response.
Main results and the role of chance: Of the 492 participants, the mean age was 33 years and the mean subfertility duration was 2.5 years. The median serum AMH was 2.1 (µg/l). The majority of patients had a suboptimal response: 326 women (66%), of whom 224 (45%) had a hypo response (defined as <two follicles sized > 15 mm) and 102 (21%) had a hyper response (defined as more than three follicles sized >15 mm). The lowest AMH category showed a trend towards a smaller risk of a suboptimal response (relative risk ratio 0.76 (95% CI 0.54, 1.06)), but this effect did not reach statistical significance. In the prediction models, BMI and serum basal FSH were significant predictors of a hypo response, while for hyper response the factors age, BMI and serum FSH were significant. A higher BMI showed a higher risk for hypo response, as did a higher FSH whereas a lower BMI and lower FSH showed a higher risk for hyper response. The addition of AMH to the models did not improve the predictive abilities.
Limitations, reasons for caution: Although the study was prospective, the main analyses were cross-sectional with characteristics measured at one time-point. The study was not powered to provide

insight into predictors of pregnancy and live births and, therefore, the result for pregnancy should be interpreted with caution.
Wider implications of the findings: This was the first large multicentre study that investigated the characteristics of ovarian response categories using standardized methods and centrally analysed laboratory measures. PRORAILS is a nationwide study with 15 hospitals and, therefore, these results are generalizable to other hospitals in the Netherlands. This study provides high-quality outcomes advancing the subfertility research field. Future studies would benefit from a randomized design investigating the effectiveness of an individualized approach versus a fixed dose. Also, the relation between a good ovarian stimulation and pregnancy rate could be further investigated.
Study funding/competing interest(s): The PRORAILS study is sponsored by Merck B.V., Schiphol-Rijk, the Netherlands, an affiliation of Merck KGaA, Darmstadt, Germany (EMR700623_612). Merck KGaA, Darmstadt, Germany, reviewed the manuscript prior to submission. The opinions remain those of the authors. Merck KGaA, Darmstadt, Germany, had no influence on the use of medication in this study. The recombinant FSH was mostly provided by Merck B.V. or MSD. F.B. is a member of the external advisory board for Merck B.V., Schiphol-Rijk, the Netherlands, and has received a research grant from Merck B.V., Schiphol-Rijk. H.v.B. is an employee from IQVIA, which is a commercial data-analysing company, and received payment for her part in the article.
Trial registration number: NCT01662180.

Gepubliceerd: Hum Reprod. 2022;37(7):1440-50.
Impact factor: 6.353 ; Q1

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8. Primary prevention of ovarian cancer: a patient decision aid for opportunistic salpingectomy
van Lieshout LAM, Gelderblom ME, de Hullu JA, The R, van Ginkel AA, Oerlemans AJM, Smeets KMWH, Schreurs MPH, Piek JMJ, Hermens RPMG.

Background: The discovery of the fallopian tube epithelium as the origin of high-grade serous ovarian cancer has brought a new option for ovarian cancer prevention. The fallopian tubes have no known function after completion of childbearing and can be removed to reduce the lifetime risk of ovarian cancer. Although the lifetime risk in the general population does not justify preventive surgery in itself, salpingectomy can be performed during abdominal surgery for other indications, also known as an opportunistic salpingectomy. The popularity of opportunistic salpingectomy is increasing worldwide; however, the variation between gynecologists and hospitals in their advice on opportunistic salpingectomy occurs because of the remaining uncertainty of evidence. Therefore, whether a woman can make her own decision depends on the hospital or gynecologist she visits. We aimed to lower this practice variation by providing standardized and unbiased counseling material.
Objective: We aimed to develop and test a patient decision aid for opportunistic salpingectomy in women undergoing pelvic gynecologic surgery to either retain the ovaries or opt for sterilization.
Study design: We followed a systematic development process based on the International Patient Decision Aid Standards. Data were collected between June 2019 and June 2020, using both qualitative and quantitative methods. The development process that occurred in collaboration with patients and healthcare professionals was overseen by a multidisciplinary steering group and was divided into 4 phases: (1) assessment of decisional needs using individual telephone interviews and questionnaires; (2) development of content and format based on decisional needs, current literature, and guidelines; (3) alpha testing and the first revision round; and (4) alpha testing and the second revision round**.**
Results: An outline of the patient decision aid was developed on the basis of decisional needs, current literature, and guidelines. It became clear that the decision aid should consist of 2 separate paths: one with information specifically for salpingectomy in addition to abdominal surgery and one for salpingectomy as a sterilization method. Both paths contained information on the anatomy and

function of ovaries and fallopian tubes, risk reduction of ovarian cancer, and potential benefits and risks of opportunistic salpingectomy. Moreover, the sterilization path contains information on various sterilization methods and risks of unwanted pregnancy. The patient decision aid was developed as an online tool that includes information chapters, a knowledge quiz, consideration statements, and a summary detailing the patient's preferences and considerations. Adjustments were made following alpha testing round 1. The improved patient decision aid was subjected to usability tests (alpha testing round 2), in which it scored an "excellent" in tests with patients and a "good" in tests with gynecologists. Furthermore, our patient decision aid met the requirements of 45 of 49 applicable items from the International Patient Decision Aid Standards criteria**.**
Conclusion: In collaboration with patients and healthcare professionals, a patient decision aid was developed on opportunistic salpingectomy and salpingectomy as a sterilization method. Both patients and gynecologists believed it is a useful tool that supports patients in making an informed decision whether to undergo an opportunistic salpingectomy and supports the counseling process by gynecologists.

Gepubliceerd: Am J Obstet Gynecol. 2022;226(2):234.e1-.e14.
Impact factor: 10.693 ; Q1

Totale impact factor: 49.569
Gemiddelde impact factor: 6.196

Aantal artikelen 1e, 2e of laatste auteur: 0
Totale impact factor: 0
Gemiddelde impact factor: 0

Heelkunde

1. Commentary on "Epidemiology, Diagnostics and Outcomes of Acute Occlusive Arterial Mesenteric Ischaemia: a Population Based Study"
Acosta S, Geelkerken RH.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2022;64(6):654-5.
Impact factor: 6.427 ; Q1

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2. Treatment Outcome Trends for Non-Ruptured Abdominal Aortic Aneurysms: A Nationwide Prospective Cohort Study
Alberga AJ, Karthaus EG, Wilschut JA, de Bruin JL, Akkersdijk GP, Geelkerken RH, Hamming JF, Wever JJ, Verhagen HJM.

Objective: The Dutch Surgical Aneurysm Audit (DSAA) initiative was established in 2013 to monitor and improve nationwide outcomes of aortic aneurysm surgery. The objective of this study was to examine whether outcomes of surgery for intact abdominal aortic aneurysms (iAAA) have improved over time**.**
Methods: Patients who underwent primary repair of an iAAA by standard endovascular (EVAR) or open surgical repair (OSR) between 2014 and 2019 were selected from the DSAA for inclusion. The primary outcome was peri-operative mortality trend per year, stratified by OSR and EVAR. Secondary outcomes were trends per year in major complications, textbook outcome (TbO), and characteristics of treated patients. The trends per year were evaluated and reported in odds ratios per year**.**
Results: In this study, 11 624 patients (74.8%) underwent EVAR and 3 908 patients (25.2%) underwent OSR. For EVAR, after adjustment for confounding factors, there was no improvement in peri-operative mortality (aOR [adjusted odds ratio] 1.06, 95% CI 0.94 - 1.20), while major complications decreased (2014: 10.1%, 2019: 7.0%; aOR 0.91, 95% CI 0.88 - 0.95) and the TbO rate increased (2014: 68.1%, 2019: 80.9%; aOR 1.13, 95% CI 1.10 - 1.16). For OSR, the peri-operative mortality decreased (2014: 6.1%, 2019: 4.6%; aOR 0.89, 95% CI 0.82 - 0.98), as well as major complications (2014: 28.6%, 2019: 23.3%; aOR 0.95, 95% CI 0.91 - 0.99). Furthermore, the proportion of TbO increased (2014: 49.1%, 2019: 58.3%; aOR 1.05, 95% CI 1.01 - 1.10). In both the EVAR and OSR group, the proportion of patients with cardiac comorbidity increased**.**
Conclusion: Since the establishment of this nationwide quality improvement initiative (DSAA), all outcomes of iAAA repair following EVAR and OSR have improved, except for peri-operative mortality following EVAR which remained unchanged.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2022;63(2):275-83.
Impact factor: 6.427 ; Q1

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3. Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With High Risk for Postoperative Complications: Results of a Randomized Clinical Trial
Berkel AEM, Bongers BC, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, Wymenga M, Bigirwamungu-Bargeman M, van der Palen J, van Det MJ, van Meeteren NLU, Klaase JM.

Objective: To assess the effects of a 3-week community-based exercise program on 30-day postoperative complications in high-risk patients scheduled for elective colorectal resection for (pre)malignancy.

Background data: Patients with a low preoperative aerobic fitness undergoing colorectal surgery have an increased risk of postoperative complications. It remains, however, to be demonstrated whether prehabilitation in these patients reduces postoperative complications**.**
Methods: This 2-center, prospective, single-blinded randomized clinical trial was carried out in 2 large teaching hospitals in the Netherlands. Patients (≥60 years) with colorectal (pre)malignancy scheduled for elective colorectal resection and with a score ≤7 metabolic equivalents on the veterans-specific activity questionnaire were randomly assigned to the prehabilitation group or the usual care group by using block-stratified randomization. An oxygen uptake at the ventilatory anaerobic threshold <11 mL/kg/min at the baseline cardiopulmonary exercise test was the final inclusion criterion. Inclusion was based on a power analysis. Patients in the prehabilitation group participated in a personalized 3-week (3 sessions per week, nine sessions in total) supervised exercise program given in community physical therapy practices before colorectal resection. Patients in the reference group received usual care. The primary outcome was the number of patients with one or more complications within 30 days of surgery, graded according to the Clavien-Dindo classification. Data were analyzed on an intention-to-treat basis**.**
Results: Between February 2014 and December 2018, 57 patients [30 males and 27 females; mean age 73.6 years (standard deviation 6.1), range 61-88 years] were randomized to either prehabilitation (n = 28) or usual care (n = 29). The rate of postoperative complications was lower in the prehabilitation group (n = 12, 42.9%) than in the usual care group (n = 21, 72.4%, relative risk 0.59, 95% confidence interval 0.37-0.96, P = 0.024).
Conclusions: Exercise prehabilitation reduced postoperative complications in high-risk patients scheduled to undergo elective colon resection for (pre)malignancy. Prehabilitation should be considered as usual care in high-risk patients scheduled for elective colon, and probably also rectal, surgery.

Gepubliceerd: Ann Surg. 2022;275(2):e299-e306.
Impact factor: 13.787 ; Q1

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4. Response to the Comments of Onerup et al and Lu and Song on: "Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With High Risk for Postoperative Complications: Results of a Randomized Clinical Trial"
Berkel AEM, Bongers BC, van Meeteren NLU, Klaase JM.

Gepubliceerd: Ann Surg. 2022;276(6):e1126-e8.
Impact factor: 13.787 ; Q1

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5. The association between preoperative body composition and aerobic fitness in patients scheduled for colorectal surgery
Berkel AEM, van Wijk L, van Dijk DPJ, Prins SN, van der Palen J, van Meeteren NLU, Olde Damink SWM, Klaase JM, Bongers BC.

Aim: Although cardiopulmonary exercise testing (CPET) is considered the gold standard, a preoperative abdominal CT scan might also provide information concerning preoperative aerobic fitness for risk assessment. This study aimed to investigate the association between preoperative CT-scan-derived body composition variables and preoperative CPET variables of aerobic fitness in colorectal surgery.
Method: In this retrospective cohort study, CT images at level L3 were analysed for skeletal muscle mass, skeletal muscle radiation attenuation, visceral adipose tissue (VAT) mass and subcutaneous adipose tissue mass. Regression analyses were performed to investigate the relation between CT-

scan-derived body composition variables, CPET-derived aerobic fitness and other preoperative patient-related variables. Logistic regression analysis was performed to predict a preoperative anaerobic threshold (AT) ≤ 11.1 ml/kg/min as cut-off for having a high risk for postoperative complications**.**
Results: Data from 78 patients (45 men; mean [SD] age 74.5 [6.4 years]) were analysed. A correlation coefficient of 0.55 was observed between absolute AT and skeletal muscle mass index. Absolute AT (R(2) of 51.1%) was lower in patients with a lower skeletal muscle mass index, together with higher age, lower body mass and higher American Society of Anesthesiologists (ASA) score. Higher ASA score (odds ratio 5.64; P = 0.033) and higher VAT mass (odds ratio 1.02; P = 0.036) were associated with an increased risk of an AT ≤ 11.1 ml/kg/min**.**
Conclusion: Body composition variables from the preoperative CT scan were moderately associated with preoperative CPET-derived aerobic fitness. Higher ASA score and higher VAT mass were associated with an increased risk of an AT ≤ 11.1 ml/kg/min.

Gepubliceerd: Colorectal Dis. 2022;24(1):93-101.
Impact factor: 3.917; Q3

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6. Coeliac Artery Release or Sham Operation in Patients Suspected of Having Median Arcuate Ligament Syndrome: The CARoSO study
Blauw JTM, Metz FM, Brusse-Keizer M, Rijnja P, Bruno MJ, Geelkerken RH.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2022;64(5):573-4.
Impact factor: 6.427 ; Q1

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7. Hypothesis of the High Mortality of Female Patients Following Elective Open Abdominal Aortic Aneurysm Repair
Bulder RMA, Tedjawirja VN, Hamming JF, Koelemay MJ, Balm R, Lindeman JHN, Study Group Collaborators: Geelkerken RH.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2022;63(5):773-4.
Impact factor: 6.427 ; Q1

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8. Breast MRI in patients after breast conserving surgery with sentinel node procedure using a superparamagnetic tracer
Christenhusz A, Pouw JJ, Simonis FFJ, Douek M, Ahmed M, Klaase JM, Dassen AE, Klazen CAH, van der Schaaf MC, Ten Haken B, Alic L.

Background: A procedure for sentinel lymph node biopsy (SLNB) using superparamagnetic iron-oxide (SPIO) nanoparticles and intraoperative sentinel lymph node (SLN) detection was developed to overcome drawbacks associated with the current standard-of-care SLNB. However, residual SPIO nanoparticles can result in void artefacts at follow-up magnetic resonance imaging (MRI) scans. We present a grading protocol to quantitatively assess the severity of these artefacts and offer an option to minimise the impact of SPIO nanoparticles on diagnostic imaging**.**
Methods: Follow-up mammography and MRI of two patient groups after a magnetic SLNB were included in the study. They received a 2-mL subareolar dose of SPIO (high-dose, HD) or a 0.1-mL intratumoural dose of SPIO (low-dose, LD). Follow-up mammography and MRI after magnetic SLNB were acquired within 4 years after breast conserving surgery (BCS). Two radiologists with over 10-

year experience in breast imaging assessed the images and analysed the void artefacts and their impact on diagnostic follow-up**.**
Results: A total of 19 patients were included (HD, n = 13; LD, n = 6). In the HD group, 9/13 patients displayed an artefact on T1-weighted images up to 3.6 years after the procedure, while no impact of the SPIO remnants was observed in the LD group.
Conclusions: SLNB using a 2-mL subareolar dose of magnetic tracer in patients undergoing BCS resulted in residual artefacts in the breast in the majority of patients, which may hamper follow-up MRI. This can be avoided by using a 0.1-mL intratumoural dose.

Gepubliceerd: Eur Radiol Exp. 2022;6(1):3.
Impact factor: 0 ; Q NVT

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9. Defining Textbook Outcome in liver surgery and assessment of hospital variation: A nationwide population-based study
de Graaff MR, Elfrink AKE, Buis CI, Swijnenburg RJ, Erdmann JI, Kazemier G, Verhoef C, Mieog JSD, Derksen WJM, van den Boezem PB, Ayez N, Liem MSL, Leclercq WKG, Kuhlmann KFD, Marsman HA, van Duijvendijk P, Kok NFM, Klaase JM, Dejong CHC, Grünhagen DJ, den Dulk M.

Introduction: Textbook outcome (TO) is a composite outcome measure covering the surgical care process in a single outcome measure. TO has an advantage over single outcome parameters with low event rates, which have less discriminating impact to detect differences between hospitals. This study aimed to assess factors associated with TO, and evaluate hospital and network variation after case-mix correction in TO rates for liver surgery**.**
Methods: This was a population-based retrospective study of all patients who underwent liver resection for malignancy in the Netherlands in 2019 and 2020. TO was defined as absence of severe postoperative complications, mortality, prolonged length of hospital stay, and readmission, and obtaining adequate resection margins. Multivariable logistic regression was used for case-mix adjustment**.**
Results: 2376 patients were included. TO was accomplished in 1380 (80%) patients with colorectal liver metastases, in 192 (76%) patients with other liver metastases, in 183 (74%) patients with hepatocellular carcinoma and 86 (51%) patients with biliary cancers. Factors associated with lower TO rates for CRLM included ASA score ≥3 (aOR 0.70, CI 0.51-0.95 p = 0.02), extrahepatic disease (aOR 0.64, CI 0.44-0.95, p = 0.02), tumour size >55 mm on preoperative imaging (aOR 0.56, CI 0.34-0.94, p = 0.02), Charlson Comorbidity Index ≥2 (aOR 0.73, CI 0.54-0.98, p = 0.04), and major liver resection (aOR 0.50, CI 0.36-0.69, p < 0.001). After case-mix correction, no significant hospital or oncological network variation was observed**.**
Conclusion: TO differs between indications for liver resection and can be used to assess between hospital and network differences.

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Impact factor: 3.184 ; Q1

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10. Post-operative Day 1 Serum Transaminase Levels in Relation to Morbidity After Liver Resection
de Klein GW, Brohet RM, Liem MSL, Klaase JM.

Background: Post-operative serum transaminases have been proposed as possible early predictors of morbidity after liver resection. This study aimed to verify the clinical value of post-operative serum transaminases**.**

Methods: Clinical data from 2001 to 2016 in a single non-academic referral HPB center were collected from a prospectively held database. Post-operative day 1 serum aspartate transaminase (AST) and alanine transaminase (ALT) were tested for their relationship with post-operative major morbidity, defined by a Clavien-Dindo score 3 or higher, and mortality**.**
Results: For this analysis, 371 patients were included, including 149 (40%) undergoing major liver resections. In total, 17% of the patients developed major morbidity. Stepwise logistic regression demonstrated that AST, and not ALT, is an independent predictor for major morbidity (p = 0.017). The probability of major morbidity significantly increased with increasing AST values. A threshold value of 242 U/L was found to be predictive for one or more major complications.
Conclusions: In this study, post-operative serum AST on day 1 was a predictive factor for major morbidity after liver resection. For patients with low AST value, early discharge could be considered. However, because of the substantial inter-individual variability of AST values, more studies are needed to translate these results into clinical practice.

Gepubliceerd: World J Surg. 2022;46(2):433-40.
Impact factor: 3.282 ; Q2

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11. A multicenter prospective cohort study to evaluate feasibility of radio-frequency identification surgical guidance for nonpalpable breast lesions: design and rationale of the RFID Localizer 1 Trial
den Dekker BM, Christenhusz A, van Dalen T, Jongen LM, van der Schaaf MC, Dassen AE, Pijnappel RM.

Background: Breast cancer screening and improving imaging techniques have led to an increase in the detection rate of early, nonpalpable breast cancers. For early breast cancer, breast conserving surgery is an effective and safe treatment. Accurate intraoperative lesion localization during breast conserving surgery is essential for adequate surgical margins while sparing surrounding healthy tissue to achieve optimal cosmesis. Preoperative wire localization and radioactive seed localization are accepted standard methods to guide surgical excision of nonpalpable breast lesions. However, these techniques present significant limitations. Radiofrequency identification (RFID) technology offers a new, nonradioactive method for localizing nonpalpable breast lesions in patients undergoing breast conserving surgery. This study aims to evaluate the feasibility of RFID surgical guidance for nonpalpable breast lesions**.**
Methods: This multicenter prospective cohort study was approved by the Institutional Review Board of the University Medical Center Utrecht. Written informed consent is obtained from all participants. Women with nonpalpable, histologically proven in situ or invasive breast cancer, who can undergo breast conserving surgery with RFID localization are considered eligible for participation. An RFID tag is placed under ultrasound guidance, up to 30 days preoperatively. The surgeon localizes the RFID tag with a radiofrequency reader that provides audible and visual real-time surgical guidance. The primary study outcome is the percentage of irradical excisions and reexcision rate, which will be compared to standards of the National Breast Cancer Organisation Netherlands (NABON)(≤ 15% irradical excisions of invasive carcinomas). Secondary outcomes include user acceptability/experiences, learning curve, duration and ease of the placement- and surgical procedure and adverse events.
Discussion: This study evaluates the feasibility of RFID surgical guidance for nonpalpable breast lesions. Results may have implications for the future localization techniques in women with nonpalpable breast cancer undergoing breast conserving surgery.
Trial registration: Netherlands National Trial Register, NL8019 , registered on September 12(th) 2019.

Gepubliceerd: BMC Cancer. 2022;22(1):305.
Impact factor: 4.638 ; Q2

12. The impact of regionalized trauma care on the distribution of severely injured patients in the Netherlands

Dijkink S, van Zwet EW, Krijnen P, Leenen LPH, Bloemers FW, Edwards MJR, Hartog DD, Leenhouts PA, Poeze M, Spanjersberg WR, Wendt KW, De Wit RJ, Van Zuthpen S, Schipper IB.

Background: Twenty years ago, an inclusive trauma system was implemented in the Netherlands. The goal of this study was to evaluate the impact of structured trauma care on the concentration of severely injured patients over time**.**
Methods: All severely injured patients (Injury Severity Score [ISS] ≥ 16) documented in the Dutch Trauma Registry (DTR) in the calendar period 2008-2018 were included for analysis. We compared severely injured patients, with and without severe neurotrauma, directly brought to trauma centers (TC) and non-trauma centers (NTC). The proportion of patients being directly transported to a trauma center was determined, as was the total Abbreviated Injury Score (AIS), and ISS**.**
Results: The documented number of severely injured patients increased from 2350 in 2008 to 4694 in 2018. During this period, on average, 70% of these patients were directly admitted to a TC (range 63-74%). Patients without severe neurotrauma had a lower chance of being brought to a TC compared to those with severe neurotrauma. Patients directly presented to a TC were more severely injured, reflected by a higher total AIS and ISS, than those directly transported to a NTC**.**
Conclusion: Since the introduction of a well-organized trauma system in the Netherlands, trauma care has become progressively centralized, with more severely injured patients being directly presented to a TC. However, still 30% of these patients is initially brought to a NTC. Future research should focus on improving pre-hospital triage to facilitate swift transfer of the right patient to the right hospital.

Gepubliceerd: Eur J Trauma Emerg Surg. 2022;48(2):1035-43.
Impact factor: 2.374 ; Q3

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13. Adherence to the Dutch Breast Cancer Guidelines for Surveillance in Breast Cancer Survivors: Real-World Data from a Pooled Multicenter Analysis

Draeger T, Voelkel V, Schreuder K, Veltman J, Dassen A, Strobbe L, Heijmans HJ, Koelemij R, Groothuis-Oudshoorn CGM, Siesling S.

Background: Regular follow-up after treatment for breast cancer is crucial to detect potential recurrences and second contralateral breast cancer in an early stage. However, information about follow-up patterns in the Netherlands is scarce.
Patients and Methods: Details concerning diagnostic procedures and policlinic visits in the first 5 years following a breast cancer diagnosis were gathered between 2009 and 2019 for 9916 patients from 4 large Dutch hospitals. This information was used to analyze the adherence of breast cancer surveillance to guidelines in the Netherlands. Multivariable logistic regression was used to relate the average number of a patient's imaging procedures to their demographics, tumor-treatment characteristics, and individual locoregional recurrence risk (LRR), estimated by a risk-prediction tool, called INFLUENCE**.**
Results: The average number of policlinic contacts per patient decreased from 4.4 in the first to 2.0 in the fifth follow-up year. In each of the 5 follow-up years, the share of patients without imaging procedures was relatively high, ranging between 31.4% and 33.6%. Observed guidelines deviations were highly significant (P < .001). A higher age, lower UICC stage, and having undergone radio- or chemotherapy were significantly associated with a higher chance of receiving an imaging procedure.

The estimated average LRR-risk was 3.5% in patients without any follow-up imaging compared with 2.3% in patients with the recommended number of 5 imagings**.**
Conclusion: Compared to guidelines, more policlinic visits were made, although at inadequate intervals, and fewer imaging procedures were performed. The frequency of imaging procedures did not correlate with the patients' individual risk profiles for LRR.

Gepubliceerd: Oncologist. 2022;27(10):e766-e73.
Impact factor: 5.837 ; Q2

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14. Severe isolated injuries have a high impact on resource use and mortality: a Dutch nationwide observational study
Driessen MLS, de Jongh MAC, Sturms LM, Bloemers FW, Ten Duis HJ, Edwards MJR, Hartog DD, Leenhouts PA, Poeze M, Schipper IB, Spanjersberg RW, Wendt KW, de Wit RJ, van Zutphen S, Leenen LPH.

Purpose: The Berlin poly-trauma definition (BPD) has proven to be a valuable way of identifying patients with at least a 20% risk of mortality, by combining anatomical injury characteristics with the presence of physiological risk factors (PRFs). Severe isolated injuries (SII) are excluded from the BPD. This study describes the characteristics, resource use and outcomes of patients with SII according to their injured body region, and compares them with those included in the BPD**.**
Methods: Data were extracted from the Dutch National Trauma Registry between 2015 and 2019. SII patients were defined as those with an injury with an Abbreviated Injury Scale (AIS) score ≥ 4 in one body region, with at most minor additional injuries (AIS ≤ 2). We performed an SII subgroup analysis per AIS region of injury. Multivariable linear and logistic regression models were used to calculate odds ratios (ORs) for SII subgroup patient outcomes, and resource needs**.**
Results: A total of 10.344 SII patients were included; 47.8% were ICU admitted, and the overall mortality was 19.5%. The adjusted risk of death was highest for external (2.5, CI 1.9-3.2) and for head SII (2.0, CI 1.7-2.2). Patients with SII to the abdomen (2.3, CI 1.9-2.8) and thorax (1.8, CI 1.6-2.0) had a significantly higher risk of ICU admission. The highest adjusted risk of disability was recorded for spine injuries (10.3, CI 8.3-12.8). The presence of ≥ 1 PRFs was associated with higher mortality rates compared to their poly-trauma counterparts, displaying rates of at least 15% for thoracic, 17% for spine, 22% for head and 49% for external SII**.**
Conclusion: A severe isolated injury is a high-risk entity and should be recognized and treated as such. The addition of PRFs to the isolated anatomical injury criteria contributes to the identification of patients with SII at risk of worse outcomes.

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Impact factor: 2.374 ; Q3

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15. The Detrimental Impact of the COVID-19 Pandemic on Major Trauma Outcomes in the Netherlands: A Comprehensive Nationwide Study
Driessen MLS, Sturms LM, Bloemers FW, Duis HJT, Edwards MJR, den Hartog D, Kuipers EJ, Leenhouts PA, Poeze M, Schipper IB, Spanjersberg RW, Wendt KW, de Wit RJ, van Zutphen S, de Jongh MAC, Leenen LPH.

Objective: To evaluate the impact of the COVID-19 pandemic on the outcome of major trauma patients in the Netherlands.

Background data: Major trauma patients highly rely on immediate access to specialized services, including ICUs, shortages caused by the impact of the COVID-19 pandemic may influence their outcome**.**
Methods: A multi-center observational cohort study, based on the Dutch National Trauma Registry was performed. Characteristics, resource usage, and outcome of major trauma patients (injury severity score ≥16) treated at all trauma-receiving hospitals during the first COVID-19 peak (March 23 through May 10) were compared with those treated from the same period in 2018 and 2019 (reference period)**.**
Results: During the peak period, 520 major trauma patients were admitted, versus 570 on average in the pre-COVID-19 years. Significantly fewer patients were admitted to ICU facilities during the peak than during the reference period (49.6% vs 55.8%; P=0.016). Patients with less severe traumatic brain injuries in particular were less often admitted to the ICU during the peak (40.5% vs 52.5%; P=0.005). Moreover, this subgroup showed an increased mortality compared to the reference period (13.5% vs 7.7%; P=0.044). These results were confirmed using multivariable logistic regression analyses. In addition, a significant increase in observed versus predicted mortality was recorded for patients who had a priori predicted mortality of 50% to 75% (P=0.012).
Conclusions: The COVID-19 peak had an adverse effect on trauma care as major trauma patients were less often admitted to ICU and specifically those with minor through moderate brain injury had higher mortality rates.

Gepubliceerd: Ann Surg. 2022;275(2):252-8.
Impact factor: 13.787 ; Q1

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16. Nationwide oncological networks for resection of colorectal liver metastases in the Netherlands: Differences and postoperative outcomes
Elfrink AKE, Kok NFM, Swijnenburg RJ, den Dulk M, van den Boezem PB, Hartgrink HH, Te Riele WW, Patijn GA, Leclercq WKG, Lips DJ, Ayez N, Verhoef C, Kuhlmann KFD, Buis CI, Bosscha K, Belt EJT, Vermaas M, van Heek NT, Oosterling SJ, Torrenga H, Eker HH, Consten ECJ, Marsman HA, Kazemier G, Wouters M, Grünhagen DJ, Klaase JM.

Introduction: Widespread differences in patient demographics and disease burden between hospitals for resection of colorectal liver metastases (CRLM) have been described. In the Netherlands, networks consisting of at least one tertiary referral centre and several regional hospitals have been established to optimize treatment and outcomes. The aim of this study was to assess variation in case-mix, and outcomes between these networks**.**
Methods: This was a population-based study including all patients who underwent CRLM resection in the Netherlands between 2014 and 2019. Variation in case-mix and outcomes between seven networks covering the whole country was evaluated. Differences in case-mix, expected 30-day major morbidity (Clavien-Dindo ≥3a) and 30-day mortality between networks were assessed**.**
Results: In total 5383 patients were included. Thirty-day major morbidity was 5.7% and 30-day mortality was 1.5%. Significant differences between networks were observed for Charlson Comorbidity Index, ASA 3+, previous liver resection, liver disease, preoperative MRI, preoperative chemotherapy, ≥3 CRLM, diameter of largest CRLM ≥55 mm, major resection, combined resection and ablation, rectal primary tumour, bilobar and extrahepatic disease. Uncorrected 30-day major morbidity ranged between 3.3% and 13.1% for hospitals, 30-day mortality ranged between 0.0% and 4.5%. Uncorrected 30-day major morbidity ranged between 4.4% and 6.0% for networks, 30-day mortality ranged between 0.0% and 2.5%. No negative outliers were observed after case-mix correction**.**

Conclusion: Variation in case-mix and outcomes are considerably smaller on a network level as compared to a hospital level. Therefore, auditing is more meaningful at a network level and collaboration of hospitals within networks should be pursued.

Gepubliceerd: Eur J Surg Oncol. 2022;48(2):435-48.
Impact factor: 3.184 ; Q1

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17. Prospective multicentre observational cohort to assess quality of life, functional outcomes and cost-effectiveness following minimally invasive surgical techniques for rectal cancer in 'dedicated centres' in the Netherlands (VANTAGE trial): a protocol
Geitenbeek R, Burghgraef T, Hompes R, Zimmerman D, Dijkgraaf M, Postma M, Ranchor A, Verheijen P, Consten E, MIRECA study group: van Duyn EB.

Introduction: Total mesorectal excision is the standard of care for rectal cancer, which can be performed using open, laparoscopic, robot-assisted and transanal technique. Large prospective (randomised controlled) trials comparing these techniques are lacking, do not take into account the learning curve and have short-term or long-term oncological results as their primary endpoint, without addressing quality of life, functional outcomes and cost-effectiveness. Comparative data with regard to these outcomes are necessary to identify the optimal minimally invasive technique and provide guidelines for clinical application.
Methods and Analysis: This trial will be a prospective observational multicentre cohort trial, aiming to compare laparoscopic, robot-assisted and transanal total mesorectal excision in adult patients with rectal cancer performed by experienced surgeons in dedicated centres. Data collection will be performed in collaboration with the prospective Dutch ColoRectal Audit and the Prospective Dutch ColoRectal Cancer Cohort. Quality of life at 1 year postoperatively will be the primary outcome. Functional outcomes, cost-effectiveness, short-term outcomes and long-term oncological outcomes will be the secondary outcomes. In total, 1200 patients will be enrolled over a period of 2 years in 26 dedicated centres in the Netherlands. The study is registered at https://www.trialregister.nl/9734 (NL9734).
Ethics and Dissemination: Data will be collected through collaborating parties, who already obtained approval by their medical ethical committee. Participants will be included in the trial after having signed informed consent. Results of this study will be disseminated to participating centres, patient organisations, (inter)national society meetings and peer-reviewed journals.

Gepubliceerd: BMJ Open. 2022;12(8):e057640.
Impact factor: 3.007; Q2

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18. Thyroid tissue in cervical lymph nodes, not always malignant
Gijsen AF, De Bruijn KMJ, Mastboom W.

Thyroid tissue in cervical lymph nodes is an interesting and rare phenomenon that cannot be directly explained by embryology. Distinguishing malignant from benign thyroid tissue in cervical lymph nodes can be challenging but is essential for treatment and might have legal implications. Patients with incidentally found thyroid tissue in cervical lymph nodes during thyroid surgery were retrospectively identified. Clinical data and findings on pathology were retrospectively collected. Two patients with thyroid tissue in cervical lymph nodes were identified. Conventional pathology complemented with immunohistochemistry and molecular diagnostics showed the thyroid tissue in cervical lymph nodes to be benign. We show that benign thyroid tissue in cervical lymph nodes can

be found in the absence or presence of a primary thyroid malignancy. A conservative approach is recommended if pathology shows benign thyroid tissue in cervical lymph nodes.

Gepubliceerd: Clin Case Rep. 2022;10(9):e6261.
Impact factor: 0; Q NVT

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19. Implementation and Outcome of Robotic Liver Surgery in the Netherlands: A Nationwide Analysis

Gorgec B, Zwart M, Nota CL, Bijlstra OD, Bosscha K, de Boer MT, de Wilde RF, Draaisma WA, Gerhards MF, Liem MS, Lips DJ, Marsman HA, Mieog JSD, Molenaar QI, Nijkamp M, Te Riele WW, Terkivatan T, Vahrmeijer AL, Besselink MG, Swijnenburg RJ, Hagendoorn J, Dutch Liver Collaborative Group.

Objective: To determine the nationwide implementation and surgical outcome of minor and major robotic liver surgery (RLS) and assess the first phase of implementation of RLS during the learning curve. SUMMARY
Background data: RLS may be a valuable alternative to laparoscopic liver surgery. Nationwide population-based studies with data on implementation and outcome of RLS are lacking**.**
Methods: Multicenter retrospective cohort study including consecutive patients who underwent RLS for all indications in nine Dutch centers (August 2014-March 2021). Data on all liver resections were obtained from the mandatory nationwide Dutch Hepato Biliary Audit (DHBA) including data from all 27 centers for liver surgery in the Netherlands. Outcomes were stratified for minor, technically major and anatomically major RLS. Learning curve effect was assessed using cumulative sum (CUSUM) analysis for blood loss**.**
Results: Of 9,437 liver resections, 400 were RLS (4.2%) procedures including 207 minor (52.2%), 141 technically major (35.3%) and 52 anatomically major (13%). The nationwide use of RLS increased from 0.2% in 2014 to 11.9% in 2020. The proportion of RLS among all minimally invasive liver resections increased from 2% to 28%. Median blood loss was 150 mL (IQR 50-350 mL) and the conversion rate 6.3% (n=25). The rate of Clavien-Dindo grade >/=III complications was 7.0% (n=27), median length of hospital stay 4 days (IQR 2-5) and 30-day/in-hospital mortality 0.8% (n=3). The R0 resection rate was 83.2% (n=263). CUSUM analysis for blood loss found a learning curve of at least 33 major RLS procedures.
Conclusions: The nationwide use of RLS in the Netherlands has increased rapidly with currently one-tenth of all liver resections and one-fourth of all minimally invasive liver resections being performed robotically. Although surgical outcomes of RLS in selected patient appear favorable, future prospective studies should determine its added value.

Gepubliceerd: Ann Surg. 2022;277(6):e1269-77.
Impact factor: 13.787 ; Q1

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20. Effectiveness and implementation of SHared decision-making supported by OUTcome information among patients with breast cancer, stroke and advanced kidney disease: SHOUT study protocol of multiple interrupted time series

Hackert MQN, Ankersmid JW, Engels N, Prick JCM, Teerenstra S, Siesling S, Drossaert CHC, Strobbe LJA, van Riet YEA, van den Dorpel RMA, Bos WJW, van der Nat PB, van den Berg-Vos RM, van Schaik SM, Garvelink MM, van der Wees PJ, van Uden-Kraan CF, Santeon VBHC breast cancer, stroke and chronic kidney disease group; Brinkman JN, Brouwers PJAM, Dassen AE.

Introduction: Within the value-based healthcare framework, outcome data can be used to inform patients about (treatment) options, and empower them to make shared decisions with their health

care professional. To facilitate shared decision-making (SDM) supported by outcome data, a multicomponent intervention has been designed, including patient decision aids on the organisation of post-treatment surveillance (breast cancer); discharge location (stroke) and treatment modality (advanced kidney disease), and training on SDM for health care professionals. The SHared decision-making supported by OUTcome information (SHOUT) study will examine the effectiveness of the intervention and its implementation in clinical practice.
Methods and Analysis: Multiple interrupted time series will be used to stepwise implement the intervention. Patients diagnosed with either breast cancer (N=630), stroke (N=630) or advanced kidney disease (N=473) will be included. Measurements will be performed at baseline, three (stroke), six and twelve (breast cancer and advanced kidney disease) months. Trends on outcomes will be measured over a period of 20 months. The primary outcome will be patients' perceived level of involvement in decision-making. Secondary outcomes regarding effectiveness will include patient-reported SDM, decisional conflict, role in decision-making, knowledge, quality of life, preferred and chosen care, satisfaction with the intervention, healthcare utilisation and health outcomes. Outcomes regarding implementation will include the implementation rate and a questionnaire on the health care professionals' perspective on the implementation process.
Ethics and Dissemination: The Medical research Ethics Committees United in Nieuwegein, the Netherlands, has confirmed that the Medical Research Involving Human Subjects Act does not apply to this study. Bureau Onderzoek & Innovatie of Santeon, the Netherlands, approved this study. The results will contribute to insight in and knowledge on the use of outcome data for SDM, and can stimulate sustainable implementation of SDM.
Trial registration number: NL8374, NL8375 and NL8376.

Gepubliceerd: BMJ Open. 2022;12(8):e055324.
Impact factor: 3.007; Q2

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21. Longitudinal Serum Protein Analysis of Women with a High Risk of Developing Breast Cancer Reveals Large Interpatient Versus Small Intrapatient Variations: First Results from the TESTBREAST Study
Hagenaars SC, Dekker LJM, Ravesteijn B, van Vlierberghe RLP, Romijn F, Verhoeff L, Witkamp AJ, Schenk KE, Keymeulen K, Menke-Pluijmers MBE, Dassen AE, Kortmann BA, de Vries J, Rutgers EJT, van der Burgt YEM, Meershoek-Klein Kranenbarg E, Cobbaert CM, Luider TM, Mesker WE, Tollenaar R.

The prospective, multicenter TESTBREAST study was initiated with the aim of identifying a novel panel of blood-based protein biomarkers to enable early breast cancer detection for moderate-to-high-risk women. Serum samples were collected every (half) year up until diagnosis. Protein levels were longitudinally measured to determine intrapatient and interpatient variabilities. To this end, protein cluster patterns were evaluated to form a conceptual basis for further clinical analyses. Using a mass spectrometry-based bottom-up proteomics strategy, the protein abundance of 30 samples was analyzed: five sequential serum samples from six high-risk women; three who developed a breast malignancy (cases) and three who did not (controls). Serum samples were chromatographically fractionated and an in-depth serum proteome was acquired. Cluster analyses were applied to indicate differences between and within protein levels in serum samples of individuals. Statistical analyses were performed using ANOVA to select proteins with a high level of clustering. Cluster analyses on 30 serum samples revealed unique patterns of protein clustering for each patient, indicating a greater interpatient than intrapatient variability in protein levels of the longitudinally acquired samples. Moreover, the most distinctive proteins in the cluster analysis were identified. Strong clustering patterns within longitudinal intrapatient samples have demonstrated the importance of identifying small changes in protein levels for individuals over time. This underlines the significance of longitudinal serum measurements, that patients can serve as their own controls,

and the relevance of the current study set-up for early detection. The TESTBREAST study will continue its pursuit toward establishing a protein panel for early breast cancer detection.

Gepubliceerd: Int J Mol Sci. 2022;23(20).
Impact factor: 4.730 ; Q1

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22. Long-term stoma-related reinterventions after anterior resection for rectal cancer with or without anastomosis: population data from the Dutch snapshot study
Hazen SJA, Vogel I, Borstlap WAA, Dekker JWT, Tuynman JB, Tanis PJ, Kusters M, Dutch Snapshot Research Group: van Duyn EB, Lips DJ.

Background: The aim of this study was to analyze the stoma-related reinterventions, complications and readmissions after an anterior resection for rectal cancer, based on a cross-sectional nationwide cohort study with 3-year follow-up**.**
Methods: Rectal cancer patients who underwent a resection with either a functional anastomosis, a defunctioned anastomosis, or Hartmann's procedure (HP) with an end colostomy in 2011 in 71 Dutch hospitals were included. The primary outcome was number of stoma-related reinterventions**.**
Results: Of the 2095 patients with rectal cancer, 1400 patients received an anterior resection and were included in this study; 257 received an initially functional anastomosis, 741 a defunctioned anastomosis, and 402 patients a HP. Of the 1400 included patients, 62% were males, 38% were females and the mean age was 67 years (SD 11.1). Following a primary functional anastomosis, 48 (19%) patients received a secondary stoma. Stoma-related complications occurred in six (2%) patients, requiring reintervention in one (0.4%) case. In the defunctioned anastomosis group, stoma-related complications were present in 92 (12%) patients, and required reintervention in 23 (3%) patients, in 10 (1%) of these more than 1 year after initial resection. Stoma-related complications occurred in 92 (23%) patients after a HP, and required reintervention in 39 (10%) patients in 17 (4%) of cases more than 1 year after initial resection. The permanent stoma rate was 11% and 20%, in the functional anastomosis and the defuctioned anastomosis group, respectively. The end colostomy in the HP group was reversed in 4% of cases.
Conclusions: Construction of a stoma after resection for rectal cancer with preservation of the sphincter is accompanied with long-term stoma-related morbidity. Stoma complications are more frequent after a HP. Even after 1 year, a significant number of reinterventions are required.

Gepubliceerd: Tech Coloproctol. 2022;26(2):99-108.
Impact factor: 3.699 ; Q1

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23. Optimising Access Surgery in Senior Haemodialysis Patients (OASIS): study protocol for a multicentre randomised controlled trial
Heggen BD, Ramspek CL, van der Bogt KEA, de Haan MW, Hemmelder MH, Hiligsmann MJC, van Loon MM, Rotmans JI, Tordoir JHM, Dekker FW, Schurink GWH, Snoeijs MGJ, Oasis Study Group: Brink HS, Willigendael EM.

Introduction: Current evidence on vascular access strategies for haemodialysis patients is based on observational studies that are at high risk of selection bias. For elderly patients, autologous arteriovenous fistulas that are typically created in usual care may not be the best option because a significant proportion of fistulas either fail to mature or remain unused. In addition, long-term complications associated with arteriovenous grafts and central venous catheters may be less relevant when considering the limited life expectancy of these patients. Therefore, we designed the

Optimising Access Surgery in Senior Haemodialysis Patients (OASIS) trial to determine the best strategy for vascular access creation in elderly haemodialysis patients.
Methods and Analysis: OASIS is a multicentre randomised controlled trial with an equal participant allocation in three treatment arms. Patients aged 70 years or older who are expected to initiate haemodialysis treatment in the next 6 months or who have started haemodialysis urgently with a catheter will be enrolled. To detect and exclude patients with an unusually long life expectancy, we will use a previously published mortality prediction model after external validation. Participants allocated to the usual care arm will be treated according to current guidelines on vascular access creation and will undergo fistula creation. Participants allocated to one of the two intervention arms will undergo graft placement or catheter insertion. The primary outcome is the number of access-related interventions required for each patient-year of haemodialysis treatment. We will enrol 195 patients to have sufficient statistical power to detect an absolute decrease of 0.80 interventions per year.
Ethics and Dissemination: Because of clinical equipoise, we believe it is justified to randomly allocate elderly patients to the different vascular access strategies. The study was approved by an accredited medical ethics review committee. The results will be disseminated through peer-reviewed publications and will be implemented in clinical practice guidelines.
Trial registration number: NL7933.

Gepubliceerd: BMJ Open. 2022;12(2):e053108.
Impact factor: 3.007; Q2

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24. Adverse health effects after breast cancer up to 14 years after diagnosis
Heins MJ, de Ligt KM, Verloop J, Siesling S, Korevaar JC, PSCCR group: Dassen AE.

Background: The number of breast cancer survivors increases, but information about long-term adverse health effects in breast cancer survivors is sparse. We aimed to get an overview of the health effects for which survivors visit their general practitioner up to 14 years after diagnosis**.**
Methods: We retrieved data on 11,671 women diagnosed with breast cancer in 2000-2016 and 23,242 age and sex matched controls from the PSCCR-Breast Cancer, a database containing data about cancer diagnosis, treatment and primary healthcare. We built Cox regression models for 685 health effects, with time until the health effect as the outcome and survivor/control and cancer treatment as predictors. Models were built separately for four age groups (aged 18/44, 45/59, 60/74 and 75/89) and two follow-up periods (1/4 and 5/14 years after diagnosis)**.**
Results: 229 health effects occurred statistically significantly more often in survivors than in controls ($p < 0.05$). Health effects varied by age, time since diagnosis and treatment, but coughing, respiratory and urinary infections, fatigue, sleep problems, osteoporosis and lymphedema were statistically significantly increased in breast cancer survivors. Osteoporosis and chest symptoms were associated with hormone therapy; respiratory and skin infections with chemotherapy and lymphedema and skin infections with axillary dissection.
Conclusions: Breast cancer survivors may experience numerous adverse health effects up to 14 years after diagnosis. Insight in individual risks may assist healthcare professionals in managing patient expectations and improve monitoring, detection and treatment of adverse health effects.

Gepubliceerd: Breast. 2022;61:22-8.
Impact factor: 4.254; Q1

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25. Short- and Long-Term Outcomes of Pancreatic Cancer Resection in Elderly Patients: A Nationwide Analysis

Henry AC, Schouten TJ, Daamen LA, Walma MS, Noordzij P, Cirkel GA, Los M, Besselink MG, Busch OR, Bonsing BA, Bosscha K, van Dam RM, Festen S, Groot Koerkamp B, van der Harst E, de Hingh I, Kazemier G, Liem MS, de Meijer VE, Nieuwenhuijs VB, Roos D, Schreinemakers JMJ, Stommel MWJ, Molenaar IQ, van Santvoort HC.

Background: The number of elderly patients with pancreatic cancer is growing, however clinical data on the short-term outcomes, rate of adjuvant chemotherapy, and survival in these patients are limited and we therefore performed a nationwide analysis**.**
Methods: Data from the prospective Dutch Pancreatic Cancer Audit were analyzed, including all patients undergoing pancreatic cancer resection between January 2014 and December 2016. Patients were classified into two age groups: <75 and ≥75 years. Major complications (Clavien-Dindo grade 3 or higher), 90-day mortality, rates of adjuvant chemotherapy, and survival were compared between age groups. Factors associated with start of adjuvant chemotherapy and survival were evaluated with logistic regression and multivariable Cox regression analysis**.**
Results: Of 836 patients, 198 were aged ≥75 years (24%) and 638 were aged <75 years (76%). Median follow-up was 38 months (interquartile range [IQR] 31-47). Major complications (31% vs. 28%; p = 0.43) and 90-day mortality (8% vs. 5%; p = 0.18) did not differ. Adjuvant chemotherapy was started in 37% of patients aged ≥75 years versus 69% of patients aged <75 years (p < 0.001). Median overall survival (OS) was 15 months (95% confidence interval [CI] 14-18) versus 21 months (95% CI 19-24; p < 0.001). Age ≥75 years was not independently associated with OS (hazard ratio 0.96, 95% CI 0.79-1.17; p = 0.71), but was associated with a lower rate of adjuvant chemotherapy (odds ratio 0.27, 95% CI 0.18-0.40; p < 0.001).
Conclusions: The rate of major complications and 90-day mortality after pancreatic resection did not differ between elderly and younger patients; however, elderly patients were less often treated with adjuvant chemotherapy and their OS was shorter.

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Impact factor: 4.339 ; Q1

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26. Laparoscopic peritoneal lavage versus sigmoidectomy for perforated diverticulitis with purulent peritonitis: three-year follow-up of the randomised LOLA trial
Hoek VT, Edomskis PP, Stark PW, Lambrichts DPV, Draaisma WA, Consten ECJ, Lange JF, Bemelman WA, LADIES trial collaborators: van Duyn EB, Lips DJ.

Background: This study aimed to compare laparoscopic lavage and sigmoidectomy as treatment for perforated diverticulitis with purulent peritonitis during a 36 month follow-up of the LOLA trial**.**
Methods: Within the LOLA arm of the international, multicentre LADIES trial, patients with perforated diverticulitis with purulent peritonitis were randomised between laparoscopic lavage and sigmoidectomy. Outcomes were collected up to 36 months. The primary outcome of the present study was cumulative morbidity and mortality. Secondary outcomes included reoperations (including stoma reversals), stoma rates, and sigmoidectomy rates in the lavage group**.**
Results: Long-term follow-up was recorded in 77 of the 88 originally included patients, 39 were randomised to sigmoidectomy (51%) and 38 to laparoscopic lavage (49%). After 36 months, overall cumulative morbidity (sigmoidectomy 28/39 (72%) versus lavage 32/38 (84%), p = 0·272) and mortality (sigmoidectomy 7/39 (18%) versus lavage 6/38 (16%), p = 1·000) did not differ. The number of patients who underwent a reoperation was significantly lower for lavage compared to sigmoidectomy (sigmoidectomy 27/39 (69%) versus lavage 17/38 (45%), p = 0·039). After 36 months, patients alive with stoma in situ was lower in the lavage group (proportion calculated from the Kaplan-Meier life table, sigmoidectomy 17% vs lavage 11%, log-rank p = 0·0268). Eventually, 17 of 38 (45%) patients allocated to lavage underwent sigmoidectomy**.**

Conclusion: Long-term outcomes showed that laparoscopic lavage was associated with less patients who underwent reoperations and lower stoma rates in patients alive after 36 months compared to sigmoidectomy. No differences were found in terms of cumulative morbidity or mortality. Patient selection should be improved to reduce risk for short-term complications after which lavage could still be a valuable treatment option.

Gepubliceerd: Surg Endosc. 2022;36(10):7764-74.
Impact factor: 3.452 ; Q2

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27. C-reactive protein (CRP) trajectory as a predictor of anastomotic leakage after rectal cancer resection: A multicentre cohort study
Hoek VT, Sparreboom CL, Wolthuis AM, Menon AG, Kleinrensink GJ, D'Hoore A, Komen N, Lange JF, APPEAL II collaborators: Lips DJ.

Aim: This study aimed to identify whether CRP-trajectory measurement, including increase in CRP-level of 50 mg/l per day, is an accurate predictor of anastomotic leakage (AL) in patients undergoing resection for rectal cancer**.**
Methods: A prospective multicentre database was used. CRP was recorded on the first three postoperative days. Sensitivity, specificity, positive and negative predictive values, and area under the receiver operator characteristic (ROC) curve were used to analyse performances of CRP-trajectory measurements between postoperative day (POD) 1-2, 2-3, 1-3 and between any two days**.**
Results: A total of 271 patients were included in the study. AL was observed in 12.5% (34/271). Increase in CRP-level of 50 mg/l between POD 1-2 had a negative predictive value of 0.92, specificity of 0.71 and sensitivity of 0.57. Changes in CRP-levels between POD 2-3 were associated with a negative predictive value, specificity and sensitivity of 0.89, 0.93 and 0.26, respectively. Changes in CRP-levels between POD 1-3 showed a negative predictive value of 0.94, specificity of 0.76 and sensitivity of 0.65. In addition, 50 mg/l changes between any two days showed a negative predictive value of 0.92, specificity of 0.66 and sensitivity of 0.62. The area under the ROC curve for all CRP-trajectory measurements ranged from 0.593-0.700**.**
Conclusion: The present study showed that CRP-trajectory between postoperative days lacks predictive value to singularly rule out AL. Early and safe discharge in patients undergoing rectal surgery for adenocarcinoma cannot be guaranteed based on this parameter. High negative predictive values are mainly caused by the relatively low prevalence of AL.

Gepubliceerd: Colorectal Dis. 2022;24(2):220-7.
Impact factor: 3.917; Q3

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28. More than 20° posterior tilt of the femoral head in undisplaced femoral neck fractures results in a four times higher risk of treatment failure
Kalsbeek J, van Walsum A, Roerdink H, Schipper I.

Purpose: In this study, we aimed to determine the correlation between the preoperative posterior tilt of the femoral head and treatment failure in patients with a Garden type I and II femoral neck fracture (FNF) treated with the dynamic locking blade plate (DLBP)**.**
Methods: Preoperative posterior tilt was measured in a prospective documented cohort of 193 patients with a Garden type I and II FNF treated with the DLBP. The correlation between preoperative posterior tilt and failure, defined as revision surgery because of avascular necrosis, non-union, or cut-out, was analyzed**.**

Results: Patients with failed fracture treatment (5.5%) had a higher degree of posterior tilt on the initial radiograph than the patients with uneventful healed fractures: 21.4° and 13.8°, respectively (p = 0.03). The failure rate was 3.2% for Garden type I and II FNF with a posterior tilt < 20° and 12.5% if the preoperative posterior tilt was ≥ 20°. A posterior tilt of ≥ 20° was associated with an odds ratio of 4.24 (95% CI 1.09-16.83; p = 0.04)**.**
Conclusion: Garden type I and II FNFs with a significant preoperative posterior tilt (≥ 20°) seem to behave like unstable fractures and have a four times higher risk of failure. Preoperative posterior tilt ≥ 20° of the femoral head should be considered as a significant predictor for failure of treatment in Garden type I and II FNFs treated with the DLBP.

Gepubliceerd: Eur J Trauma Emerg Surg. 2022;48(2):1343-50.
Impact factor: 2.374 ; Q3

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29. Cost Effectiveness of Splenic Artery Embolization versus Splenectomy after Trauma in the Netherlands
Kanters TA, Raaijmakers C, Lohle PNM, de Vries J, Hakkaart-van Roijen L, SPLENIQ study group: de Wit RJ, Klazen CAH.

Purpose: To demonstrate that splenic artery embolization (SAE) is more cost-effective than splenectomy from a societal perspective in the Netherlands.
Material and Methods: Patient-level data obtained from the SPLENIQ study were used to populate a health economic model and were supplemented with expert opinion when necessary. Propensity score matching was used to correct for baseline differences in injury severity scores. The health economic model consisted of 3 health states (complications after intervention, SAE failure, and recovery) and a dead state. Model outcomes were incremental quality-adjusted life years (QALYs) and incremental costs of SAE over splenectomy. The Dutch health economic guidelines were followed. The model used a lifetime time horizon. Uncertainty was assessed using probabilistic sensitivity analysis and scenario analyses**.**
Results: Patients undergoing SAE had a higher life expectancy than patients undergoing splenectomy. Incremental QALYs were 3.1 (mostly explained by difference in life expectancy), and incremental costs were €34,135 (explained by costs related to medical consumption and lost productivity in additional life years), leading to an incremental cost-effectiveness ratio of €11,010 per QALY. SAE was considered cost-effective in >95% of iterations using a threshold of €20,000 per QALY.
Conclusions: SAE results in more QALYs than splenectomy. Intervention costs for SAE are lower than that for splenectomy, but medical consumption and productivity costs in later years are higher for SAE due to better survival. SAE was found to be cost-effective compared with splenectomy under appropriate Dutch cost-effectiveness thresholds.

Gepubliceerd: J Vasc Interv Radiol. 2022;33(4):392-8.e4.
Impact factor: 3.682 ; Q2

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30. Hospital variation and outcomes of simultaneous resection of primary colorectal tumour and liver metastases: a population-based study
Krul MF, Elfrink AKE, Buis CI, Swijnenburg RJ, Te Riele WW, Verhoef C, Gobardhan PD, Dulk MD, Liem MSL, Tanis PJ, Mieog JSD, van den Boezem PB, Leclercq WKG, Nieuwenhuijs VB, Gerhards MF, Klaase JM, Grünhagen DJ, Kok NFM, Kuhlmann KFD.

Background: The optimal treatment sequence for patients with synchronous colorectal liver metastases (CRLM) remains uncertain. This study aimed to assess factors associated with the use of simultaneous resections and impact on hospital variation.
Method: This population-based study included all patients who underwent liver surgery for synchronous colorectal liver metastases between 2014 and 2019 in the Netherlands. Factors associated with simultaneous resection were identified. Short-term surgical outcomes of simultaneous resections and factors associated with 30-day major morbidity were evaluated**.**
Results: Of 2146 patients included, 589 (27%) underwent simultaneous resection in 28 hospitals. Simultaneous resection was associated with age, sex, BMI, number, size and bilobar distribution of CRLM, and administration of preoperative chemotherapy. More minimally invasive and minor resections were performed in the simultaneous group. Hospital variation was present (range 2.4%-83.3%) with several hospitals performing simultaneous procedures more and less frequently than expected. Simultaneous resection resulted in 13% 30-day major morbidity, and 1% mortality. ASA classification ≥3 was independently associated with higher 30-day major morbidity after simultaneous resection (aOR 1.97, CI 1.10-3.42, p = 0.018)**.**
Conclusion: Distinctive patient and tumour characteristics influence the choice for simultaneous resection. Remarkable hospital variation is present in the Netherlands.

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Impact factor: 3.842 ; Q1

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31. Incidence and predictive factors for endograft limb patency of the fenestrated Anaconda endograft used for complex endovascular aneurysm repair
Leeuwerke SJG, de Niet A, Geelkerken RH, Reijnen M, Zeebregts CJ.

Objective: In the present study, we have described the incidence, risk factors, and outcomes of treatment of limb occlusion for patients who had undergone treatment of complex thoracoabdominal aortic aneurysms with the fenestrated Anaconda endograft (Terumo Aortic, Inchinnan, UK)**.**
Methods: Between June 2010 and May 2018, 335 patients had undergone elective fenestrated aortic aneurysm repair at 11 participating centers using the fenestrated Anaconda endograft with a median follow-up of 14.3 months (interquartile range, 27.4 months). The primary outcome measure was freedom from limb occlusion. The secondary outcome measures were freedom from limb-related reintervention, secondary patency, and the risk factors associated with limb occlusion**.**
Results: Of the 335 patients, 30 (9.0%) had presented with limb occlusion during follow-up with a freedom from limb occlusion rate of 98.5%, 91.2%, and 81.7% at 30 days and 1 and 5 years, respectively. In 87% of the cases, no obvious cause for limb occlusion was documented. Primary occlusion had occurred within 30 days in 36.7% and within 1 year in 80.0%. Of the 30 patients, 23 (77%) had undergone an occlusion-related reintervention and 7 (23.3%) had been treated conservatively. The freedom from limb occlusion-related reintervention at 30 days and 1 and 5 years was 97.8%, 93.2%, and 88.6%, respectively. Secondary patency was 91.3% after 1 month and 86.2% after 1 and 5 years. Female sex (odds ratio [OR], 3.27; 95% confidence interval [CI], 1.28-8.34; P = .01) was a statistically significant predictor for limb occlusion. A greater proportion of thrombus in the aneurysm sac appeared to be protective for limb occlusion (0% vs <25%: OR, 0.22; 95% CI, 0.07-0.63; P = .01; 0% vs 25%-50%: OR, 0.20; 95% CI, 0.07-0.57; P = .00; and 0% vs >50%: OR, 0.08; 95% CI, 0.02-0.38; P = .00), as did iliac angulation (OR, 0.99; 95% CI, 0.98-1.00; P = .04).
Conclusions: Limb occlusion remains a significant impediment of endograft durability for patients treated with the fenestrated Anaconda endograft, especially for female patients. In contrast, a high aneurysmal thrombus load and a high degree of iliac angulation appeared to be protective for limb occlusion, for which no obvious cause could be identified.

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Impact factor: 4.860 ; Q1

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32. Prevalence of inflicted and neglectful femur shaft fractures in young children in national level I trauma centers
Loos MHJ, Bakx R, Allema JH, Bloemers FW, Ten Bosch JA, Edwards MJR, Hulscher JBF, Keyzer-Dekker CMG, Krug E, de Ridder VA, Spanjersberg WR, Teeuw AH, Theeuwes HP, de Vries S, de Wit R, van Rijn RR.

Background: The prevalence of inflicted femur fractures in young children varies (1.5-35.2%), but these data are based on small retrospective studies with high heterogeneity. Age and mobility of the child seem to be indicators of inflicted trauma.
Objective: This study describes other factors associated with inflicted and neglectful trauma that can be used to distinguish inflicted and neglectful from accidental femur fractures.
Material and Methods: This retrospective study included children (0-6 years) who presented with an isolated femur fracture at 1 of the 11 level I trauma centers in the Netherlands between January 2010 and January 2016. Outcomes were classified based on the conclusions of the Child Abuse and Neglect teams or the court. Cases in which conclusions were unavailable and there was no clear accidental cause were reviewed by an expert panel**.**
Results: The study included 328 children; 295 (89.9%) cases were classified as accidental trauma. Inflicted trauma was found in 14 (4.3%), while 19 (5.8%) were cases of neglect. Indicators of inflicted trauma were age 0-5 months (29%, positive likelihood ratio [LR +] 8.35), 6-12 months (18%, LR + 5.98) and 18-23 months (14%, LR + 3.74). Indicators of neglect were age 6-11 months (18%, LR + 4.41) and age 18-23 months (8%, LR + 1.65). There was no difference in fracture morphology among groups**.**
Conclusion: It is unlikely that an isolated femur fracture in ambulatory children age > 24 months is caused by inflicted trauma/neglect. Caution is advised in children younger than 24 months because that age is the main factor associated with inflicted trauma/neglect and inflicted femur fractures.

Gepubliceerd: Pediatr Radiol. 2022;52(12):2359-67.
Impact factor: 3.005 ; Q2

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33. The prevalence of non-accidental trauma among children with polytrauma: A nationwide level-I trauma centre study
Loos MHJ, van Rijn RR, Krug E, Bloemers FW, Ten Bosch JA, Bossuyt PMM, Edwards MJR, Greeven APA, Hulscher JBF, Keyzer-Dekker CMG, de Ridder VA, Spanjersberg WR, Teeuw AH, Theeuwes HP, de Vries S, de Wit R, Bakx R.

Objective: We aimed to investigate the prevalence and characteristics of non-accidental trauma (NAT) in children with polytrauma treated at level-I trauma centres (TC). SUMMARY OF **Background:** Data 6-10% Of children who present at the emergency department with injuries, sustain polytrauma. Polytrauma may result from either accidental (AT) or NAT, i.e. inflicted or neglect. The prevalence of NAT among children with polytrauma is currently unclear**.**
Methods: This is a retrospective study that included children (0-18 years) with an Injury Severity Score >15, who presented at one of the 11 Level-I trauma centers (TC) in the Netherlands between January 1, 2010 and January 1, 2016. Outcomes were classified based on the conclusions of the Child Abuse and Neglect-team. Cases in which conclusions were unavailable and there was no clear accidental cause of injuries were reviewed by an expert panel**.**

Results: The study included 1623 children, 1452 (89%) were classified as AT, 171 (11%) as NAT; 39 (2,4%) inflicted and 132 (8,1%) neglect. Of pre-school aged children (<5 years) 41% sustained NAT (OR26.73, 95%CI 17.70-40.35), 35/342 (10%) inflicted and 104/342 (31%) neglect. Admission due to 'cardiopulmonary arrest' was the result of inflicted trauma (30% vs 0%,p < 0.001). NAT had a higher mortality rate (16% vs 10%, p = 0.006). Indicators of NAT were: (near-)drowning (OR10.74, 95%CI 5.94-19.41), burn (OR8.62, 95%CI 4.08-18.19) and fall from height (OR2.18, 95%CI 1.56-3.02).
Conclusions: NAT was the cause of polytrauma in 11% of children in our nationwide level-I TC study; 41% of these polytrauma were the result of NAT experienced by preschool-aged children. Our data show the importance of awareness for NAT.

Gepubliceerd: J Forensic Leg Med. 2022;90:102386.
Impact factor: 1.692 ; Q3

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34. A scoring system for predicting malignancy in intraductal papillary mucinous neoplasms of the pancreas: a multicenter EUROPEAN validation
Manuel-Vázquez A, Balakrishnan A, Agami P, Andersson B, Berrevoet F, Besselink MG, Boggi U, Caputo D, Carabias A, Carrion-Alvarez L, Franco CC, Coppola A, Dasari BVM, Diaz-Mercedes S, Feretis M, Fondevila C, Fusai GK, Garcea G, Gonzabay V, Bravo MÁ G, Gorris M, Hendrikx B, Hidalgo-Salinas C, Kadam P, Karavias D, Kauffmann E, Kourdouli A, La Vaccara V, van Laarhoven S, Leighton J, Liem MSL, Machairas N, Magouliotis D, Mahmoud A, Marino MV, Massani M, Requena PM, Mentor K, Napoli N, Nijhuis JHT, Nikov A, Nistri C, Nunes V, Ruiz EO, Pandanaboyana S, Saborido BP, Pohnán R, Popa M, Pérez BS, Bueno FS, Serrablo A, Serradilla-Martín M, Skipworth JRA, Soreide K, Symeonidis D, Zacharoulis D, Zelga P, Aliseda D, Santiago MJC, Mancilla CF, Fragua RL, Hughes DL, Llorente CP, Lesurtel M, Gallagher T, Ramia JM.

Purpose: A preoperative estimate of the risk of malignancy for intraductal papillary mucinous neoplasms (IPMN) is important. The present study carries out an external validation of the Shin score in a European multicenter cohort**.**
Methods: An observational multicenter European study from 2010 to 2015. All consecutive patients undergoing surgery for IPMN at 35 hospitals with histological-confirmed IPMN were included**.**
Results: A total of 567 patients were included. The score was significantly associated with the presence of malignancy (p < 0.001). In all, 64% of the patients with benign IPMN had a Shin score < 3 and 57% of those with a diagnosis of malignancy had a score ≥ 3. The relative risk (RR) with a Shin score of 3 was 1.37 (95% CI: 1.07-1.77), with a sensitivity of 57.1% and specificity of 64.4%**.**
Conclusion: Patients with a Shin score ≤ 1 should undergo surveillance, while patients with a score ≥ 4 should undergo surgery. Treatment of patients with Shin scores of 2 or 3 should be individualized because these scores cannot accurately predict malignancy of IPMNs. This score should not be the only criterion and should be applied in accordance with agreed clinical guidelines.

Gepubliceerd: Langenbecks Arch Surg. 2022;407(8):3447-55.
Impact factor: 2.895 ; Q2

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35. Systematic Review of the Efficacy of Treatment for Median Arcuate Ligament Syndrome
Metz FM, Blauw JTM, Brusse-Keizer M, Kolkman JJ, Bruno MJ, Geelkerken RH.

Objective: Since the first description of the median arcuate ligament syndrome (MALS), the existence for the syndrome and the efficacy of treatment for it have been questioned**.**
Methods: A systematic review conforming to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement was conducted, with a broader view on treatment for MALS

including any kind of coeliac artery release, coeliac plexus resection, and coeliac plexus blockage, irrespective of age. Online databases were used to identify papers published between 1963 and July 2021. The inclusion criteria were abdominal symptoms, proof of MALS on imaging, and articles reporting at least three patients. Primary outcomes were symptom relief and quality of life (QoL)**.**
Results: Thirty-eight studies describing 880 adult patients and six studies describing 195 paediatric patients were included. The majority of the adult studies reported symptom relief of more than 70% from three to 228 months after treatment. Two adult studies showed an improved QoL after treatment. Half of the paediatric studies reported symptom relief of more than 70% from six to 62 months after laparoscopic coeliac artery release, and four studies reported an improved QoL. Thirty-five (92%) adult studies and five (83%) paediatric studies scored a high or unclear risk of bias for the majority of the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) items. The meaning of coeliac plexus resection or blockage could not be substantiated**.**
Conclusion: This systematic review suggests a sustainable symptom relief of more than 70% after treatment for MALS in the majority of adult and paediatric studies; however, owing to the heterogeneity of the inclusion criteria and outcome parameters, the risk of bias was high and a formal meta-analysis could not be performed. To improve care for patients with MALS the next steps would be to deal with reporting standards, outcome definitions, and consensus descriptions of the intervention(s), after which an appropriate randomised controlled trial should be performed.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2022;64(6):720-32.
Impact factor: 6.427 ; Q1

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36. Outcome after percutaneous coronary intervention with contemporary stents in patients with concomitant peripheral arterial disease: A patient-level pooled analysis of four randomized trials
Pinxterhuis TH, Ploumen EH, Zocca P, Doggen CJM, Schotborgh CE, Anthonio RL, Roguin A, Danse PW, Benit E, Aminian A, Stoel MG, Linssen GCM, Geelkerken RH, von Birgelen C.

Background and Aims: A considerable number of patients who undergo percutaneous coronary intervention (PCI) also have peripheral arterial disease (PAD) - a signal of more advanced atherosclerosis. After bare metal and early-generation drug-eluting coronary stent implantation, PAD patients showed inferior outcome. As stents and medical treatment were further improved, we aimed to assess the impact of PAD on outcome of PCI with contemporary new-generation stents**.**
Methods: We analyzed 3-year pooled patient-level data from 4 large-scale randomized new-generation stent trials to compare all-comer patients with and without (core lab-verified) history of symptomatic PAD, defined as obstructive lesions in peripheral locations including lower and upper extremities, carotid, vertebral, mesenteric and renal arteries. Main endpoint was target vessel failure: cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization**.**
Results: Of all 9204 patients, 695 (7.6%) had a history of symptomatic PAD. They were older and had more often diabetes, renal failure, hypertension, hypercholesterolemia, and prior stroke. PAD was an independent risk factor for target vessel failure (adjusted-HR:1.42, 95%-CI:1.12-1.73, p = 0.001). Target vessel revascularization (adjusted-HR:1.37, 95%-CI:1.04-1.80, p = 0.026), death (adjusted-HR:1.52, 95%-CI:1.17-1.99, p = 0.002), and major adverse cardiovascular event risks (adjusted-HR:1.36, 95%-CI:1.13-1.64, p = 0.001) were also substantially higher.
Conclusions: A history of symptomatic PAD still allows to simply identify patients with increased risk of unfavorable clinical outcome after PCI, including a higher risk of repeated coronary revascularization, despite using contemporary stents. In clinical practice, this knowledge about higher event risks of PAD patients is helpful both during Heart Team discussions and when informing patients about the procedural risk.

Gepubliceerd: Atherosclerosis. 2022;355:52-9.
Impact factor: 6.851 ; Q1

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37. A Comparison of Health Status and Quality of Life in Patients with Intermittent Claudication
Roijers JP, van den Houten MML, Hopmans CJ, Vriens P, Willigendael EM, Lodder P, de Vries J, Teijink JAW, van der Laan L.

Background: Patient reported outcome measures (PROMs) such as health status (HS) and quality of life (QOL) are frequently used interchangeably while they represent different outcomes. Whether a discrepancy exists in patients with intermittent claudication (IC) in changes over time between HS and QOL is unclear. This study aimed to investigate the strength and the direction of the association between HS and QOL over time in patients with IC that underwent supervised exercise therapy (SET).
Material and Methods: Patients were part of the ELECT multi-center prospective cohort study. One goal of this study was to obtain data on HS and QOL at different time intervals of patients with IC that underwent SET. HS (VascuQOL-6) and QOL (WHOQOL-BREF) were completed at baseline, 3 months, and 6 months follow up. Pearson's correlation coefficients and the associated common variances (R(2)) were calculated to measure the strength and the direction of the association between HS and QOL in changes between baseline and follow-up moments**.**
Results: In total, 177 patients were included in data analyses. Only changes in physical QOL and overall QOL had a small correlation with changes over time in HS, at both 3- and 6 months follow up (respectively R(2)=.14; P < 0.001 and R(2) = 0.12; P < 0.001 for physical QOL and R(2) = 0.18; P < 0.001 and R(2) = 0.13; P < 0.001 for overall QOL).
Conclusions: This study showed that HS and QOL provide different outcomes in patients with IC that underwent SET. Future studies should be aware of these differences before PROMs are being incorporated as an outcome measure in clinical studies.

Gepubliceerd: Ann Vasc Surg. 2022;78:302-9.
Impact factor: 1.607 ; Q4

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38. The many faces of diabetes. Is there a need for re-classification? A narrative review
Sakran N, Graham Y, Pintar T, Yang W, Kassir R, Willigendael EM, Singhal R, Kooreman ZE, Ramnarain D, Mahawar K, Parmar C, Madhok B, Pouwels S.

The alarming rise in the worldwide prevalence of obesity and associated type 2 diabetes mellitus (T2DM) have reached epidemic portions. Diabetes in its many forms and T2DM have different physiological backgrounds and are difficult to classify. Bariatric surgery (BS) is considered the most effective treatment for obesity in terms of weight loss and comorbidity resolution, improves diabetes, and has been proven superior to medical management for the treatment of diabetes. The term metabolic surgery (MS) describes bariatric surgical procedures used primarily to treat T2DM and related metabolic conditions. MS is the most effective means of obtaining substantial and durable weight loss in individuals with obesity. Originally, BS was used as an alternative weight-loss therapy for patients with severe obesity, but clinical data revealed its metabolic benefits in patients with T2DM. MS is more effective than lifestyle or medical management in achieving glycaemic control, sustained weight loss, and reducing diabetes comorbidities. New guidelines for T2DM expand the use of MS to patients with a lower body mass index.Evidence has shown that endocrine changes resulting from BS translate into metabolic benefits that improve the comorbid conditions associated with obesity, such as hypertension, dyslipidemia, and T2DM. Other changes include bacterial flora rearrangement, bile acids secretion, and adipose tissue effect.This review aims to

examine the physiological mechanisms in diabetes, risks for complications, the effects of bariatric and metabolic surgery and will shed light on whether diabetes should be reclassified.

Gepubliceerd: BMC Endocr Disord. 2022;22(1):9.
Impact factor: 3.263 ; Q3

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39. Retrospective evaluation of national MRI reporting quality for lateral lymph nodes in rectal cancer patients and concordance with prospective re-evaluation following additional training
Sluckin TC, Hazen SJA, Horsthuis K, Beets-Tan RGH, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group: Hendriksen EM, van Duyn EB.

Objectives: The presence and size of lateral lymph nodes (LLNs) are important factors influencing treatment decisions for rectal cancer. Awareness of the clinical relevance and describing LLNs in MRI reports is therefore essential. This study assessed whether LLNs were mentioned in primary MRI reports at a national level and investigated the concordance with standardised re-review**.**
Methods: This national, retrospective, cross-sectional cohort study included 1096 patients from 60 hospitals treated in 2016 for primary cT3-4 rectal cancer ≤ 8 cm from the anorectal junction. Abdominal radiologists re-reviewed all MR images following a 2-h training regarding LLNs**.**
Results: Re-review of MR images identified that 41.0% of enlarged (≥ 7 mm) LLNs were not mentioned in primary MRI reports. A contradictory anatomical location was stated for 73.2% of all LLNs and a different size (≥/< 7 mm) for 41.7%. In total, 49.4% of all cases did not mention LLNs in primary MRI reports. Reporting LLNs was associated with stage (cT3N0 44.3%, T3N+/T4 52.8%, p = 0.013), cN stage (N0 44.1%, N1 48.6%, N2 59.5%, p < 0.001), hospital type (non-teaching 34.6%, teaching 52.2%, academic 53.2% p = 0.006) and annual rectal cancer resection volumes (low 34.8%, medium 47.7%, high 57.3% p < 0.001). For LLNs present according to original MRI reports (n = 226), 64.2% also mentioned a short-axis size, 52.7% an anatomical location and 25.2% whether it was deemed suspicious.
Conclusions: Almost half of the primary MRI reports for rectal cancer patients treated in the Netherlands in 2016 did not mention LLNs. A significant portion of enlarged LLNs identified during re-review were also not mentioned originally, with considerable discrepancies for location and size. These results imply insufficient awareness and indicate the need for templates, education and training.

Gepubliceerd: Insights Imaging. 2022;13(1):171.
Impact factor: 5.036 ; Q2

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40. Algorithm-based care versus usual care for the early recognition and management of complications after pancreatic resection in the Netherlands: an open-label, nationwide, stepped-wedge cluster-randomised trial
Smits FJ, Henry AC, Besselink MG, Busch OR, van Eijck CH, Arntz M, Bollen TL, van Delden OM, van den Heuvel D, van der Leij C, van Lienden KP, Moelker A, Bonsing BA, Borel Rinkes IH, Bosscha K, van Dam RM, Derksen WJM, den Dulk M, Festen S, Groot Koerkamp B, de Haas RJ, Hagendoorn J, van der Harst E, de Hingh IH, Kazemier G, van der Kolk M, Liem M, Lips DJ, Luyer MD, de Meijer VE, Mieog JS, Nieuwenhuijs VB, Patijn GA, Te Riele WW, Roos D, Schreinemakers JM, Stommel MWJ, Wit F, Zonderhuis BA, Daamen LA, van Werkhoven CH, Molenaar IQ, van Santvoort HC.

Background: Early recognition and management of postoperative complications, before they become clinically relevant, can improve postoperative outcomes for patients, especially for high-risk procedures such as pancreatic resection**.**

Methods: We did an open-label, nationwide, stepped-wedge cluster-randomised trial that included all patients having pancreatic resection during a 22-month period in the Netherlands. In this trial design, all 17 centres that did pancreatic surgery were randomly allocated for the timing of the crossover from usual care (the control group) to treatment given in accordance with a multimodal, multidisciplinary algorithm for the early recognition and minimally invasive management of postoperative complications (the intervention group). Randomisation was done by an independent statistician using a computer-generated scheme, stratified to ensure that low-medium-volume centres alternated with high-volume centres. Patients and investigators were not masked to treatment. A smartphone app was designed that incorporated the algorithm and included the daily evaluation of clinical and biochemical markers. The algorithm determined when to do abdominal CT, radiological drainage, start antibiotic treatment, and remove abdominal drains. After crossover, clinicians were trained in how to use the algorithm during a 4-week wash-in period; analyses comparing outcomes between the control group and the intervention group included all patients other than those having pancreatic resection during this wash-in period. The primary outcome was a composite of bleeding that required invasive intervention, organ failure, and 90-day mortality, and was assessed by a masked adjudication committee. This trial was registered in the Netherlands Trial Register, NL6671**.**
Findings: From Jan 8, 2018, to Nov 9, 2019, all 1805 patients who had pancreatic resection in the Netherlands were eligible for and included in this study. 57 patients who underwent resection during the wash-in phase were excluded from the primary analysis. 1748 patients (885 receiving usual care and 863 receiving algorithm-centred care) were included. The primary outcome occurred in fewer patients in the algorithm-centred care group than in the usual care group (73 [8%] of 863 patients vs 124 [14%] of 885 patients; adjusted risk ratio [RR] 0·48, 95% CI 0·38-0·61; p<0·0001). Among patients treated according to the algorithm, compared with patients who received usual care there was a decrease in bleeding that required intervention (47 [5%] patients vs 51 [6%] patients; RR 0·65, 0·42-0·99; p=0·046), organ failure (39 [5%] patients vs 92 [10%] patients; 0·35, 0·20-0·60; p=0·0001), and 90-day mortality (23 [3%] patients vs 44 [5%] patients; 0·42, 0·19-0·92; p=0·029).
Interpretation: The algorithm for the early recognition and minimally invasive management of complications after pancreatic resection considerably improved clinical outcomes compared with usual care. This difference included an approximate 50% reduction in mortality at 90 days. FUNDING: The Dutch Cancer Society and UMC Utrecht.

Gepubliceerd: Lancet. 2022;399(10338):1867-75.
Impact factor: 202.731 ; Q1

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41. Optimal postoperative pain management after VATS lung resection by thoracic epidural analgesia, continuous paravertebral block or single-shot intercostal nerve block (OPtriAL): study protocol of a three-arm multicentre randomised controlled trial
Spaans LN, Dijkgraaf MGW, Meijer P, Mourisse J, Bouwman RA, Verhagen A, van den Broek FJC, OPtriAL study group: van Duyn EB, Potters JW.

Background: Adequate pain control after video-assisted thoracoscopic surgery (VATS) for lung resection is important to improve postoperative mobilisation, recovery, and to prevent pulmonary complications. So far, no consensus exists on optimal postoperative pain management after VATS anatomic lung resection. Thoracic epidural analgesia (TEA) is the reference standard for postoperative pain management following VATS. Although the analgesic effect of TEA is clear, it is associated with patient immobilisation, bladder dysfunction and hypotension which may result in delayed recovery and longer hospitalisation. These disadvantages of TEA initiated the development of unilateral regional techniques for pain management. The most frequently used techniques are continuous paravertebral block (PVB) and single-shot intercostal nerve block (ICNB). We hypothesize

that using either PVB or ICNB is non-inferior to TEA regarding postoperative pain and superior regarding quality of recovery (QoR). Signifying faster postoperative mobilisation, reduced morbidity and shorter hospitalisation, these techniques may therefore reduce health care costs and improve patient satisfaction**.**
Methods: This multi-centre randomised study is a three-arm clinical trial comparing PVB, ICNB and TEA in a 1:1:1 ratio for pain (non-inferiority) and QoR (superiority) in 450 adult patients undergoing VATS anatomic lung resection. Patients will not be eligible for inclusion in case of contraindications for TEA, PVB or ICNB, chronic opioid use or if the lung surgeon estimates a high probability that the operation will be performed by thoracotomy.
Primary outcomes: (1) the proportion of pain scores >/= 4 as assessed by the numerical rating scale (NRS) measured during postoperative days (POD) 0-2; and (2) the QoR measured with the QoR-15 questionnaire on POD 1 and 2. Secondary outcome measures are cumulative use of opioids and analgesics, postoperative complications, hospitalisation, patient satisfaction and degree of mobility.
Discussion: The results of this trial will impact international guidelines with respect to perioperative care optimization after anatomic lung resection performed through VATS, and will determine the most cost-effective pain strategy and may reduce variability in postoperative pain management. Trial registration The trial is registered at the Netherlands Trial Register (NTR) on February 1st, 2021 (NL9243). The NTR is no longer available since June 24th, 2022 and therefore a revised protocol has been registered at ClinicalTrials.gov on August 5th, 2022 (NCT05491239).
Protocol version: version 3 (date 06-05-2022), ethical approval through an amendment (see ethical proof in the Study protocol proof).

Gepubliceerd: BMC Surg. 2022;22(1):330.
Impact factor: 2.030; Q3

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42. Mortality following elective abdominal aortic aneurysm repair in women
Tedjawirja VN, Alberga AJ, Hof MHP, Vahl AC, Koelemay MJW, Balm R, Dutch Society of Vascular Surgery: Menting TP, Beuk RJ, Geelkerken RH, Meerwald R, Willigendael EM.

Background: Previous studies have focused on patient-related risk factors to explain the higher mortality risk in women undergoing elective abdominal aortic aneurysm (AAA) repair. The aim of this study was to evaluate whether hospital-related factors influence outcomes following AAA repair in women**.**
Methods: Patients undergoing elective AAA repair in 61 hospitals in the Netherlands were identified from the Dutch Surgical Aneurysm Audit registry (2013-2018). A mixed-effects logistic regression analysis was conducted to assess the effect of sex on in-hospital and/or 30-day mortality. This analysis accounted for possible correlation of outcomes among patients who were treated in the same hospital, by adding a hospital-specific random effect to the statistical model. The analysis adjusted for patient-related risk factors and hospital volume of open surgical repair (OSR) and endovascular aneurysm repair (EVAR)**.**
Results: Some 12 034 patients were included in the analysis. The mortality rate was higher in women than among men: 53 of 1780 (3.0 per cent) versus 152 of 10 254 (1.5 per cent) respectively. Female sex was significantly associated with mortality after correction for patient- and hospital-related factors (odds ratio 1.68, 95 per cent c.i. 1.20 to 2.37). OSR volume was associated with lower mortality (OR 0.91 (0.85 to 0.95) per 10-procedure increase) whereas no such relationship was identified with EVAR volume (OR 1.03 (1.01 to 1.05) per 10-procedure increase)**.**
Conclusion: Women are at higher risk of death after abdominal aortic aneurysm repair irrespective of patient- and hospital-related factors.

Gepubliceerd: Br J Surg. 2022;109(4):340-5.

Impact factor: 11.782; Q1

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43. Identifying Women at High Risk of 90 Day Death after Elective Open Abdominal Aortic Aneurysm Repair: A Multicentre Case Control Study
Tedjawirja VN, Bulder RMA, Lindeman JHN, Hamming JF, van Dieren S, Balm R, Koelemay MJW, Study Group Collaborators: Geelkerken RH, Leeuwerke SJG.

Objective: The aim of this study was to identify risk factors for 90 day death after elective open surgical repair (OSR) of abdominal aortic aneurysms (AAAs) in women**.**
Methods: This was a multicentre case control study. The nationwide Dutch Surgical Aneurysm Audit registry (2013-2019) was solely used to identify women who underwent elective OSR as eligible patients. Data for this study were subsequently collected from the patients' medical files. Women with AAA were included and those who died (cases) were compared with those who survived (controls) 90 days after surgery. Inflammatory, mycotic, or symptomatic or ruptured AAA were excluded. The association between pre- and peri-operative risk factors and death was assessed by logistic regression analysis in the whole sample and after matching cases to controls of the same age at the time of repair. Mesenteric artery patency was also assessed on pre-operative comdputed tomography and used in the analysis**.**
Results: In total, 266 patients (30 cases and 236 controls) from 21 hospitals were included. Cases were older (median [interquartile range; IQR] 75 years [71, 78.3] vs. 71 years [66, 77]; p = .002) and more often had symptomatic peripheral arterial disease (PAD) (14/29 [48%] vs. 49/227 [22%]; p = .002). Intra-operative blood loss (median [IQR] 1.6 L [1.1, 3.0] vs. 1.2 L [0.7, 1.8]), acute myocardial infarction (AMI) (10/30 [33%] vs. 8/236 [3%]), renal failure (17/30 [57%] vs. 33/236 [14%]), and bowel ischaemia (BI) (17/29 [59%] vs. 12/236 [5%]) were more prevalent among cases. Older age (odds ratio [OR] 1.11, 95% confidence interval [CI] 1.03-1.19) and PAD (OR 3.91, 95% CI 1.57-9.74) were associated with death. Multivariable analysis demonstrated that, after adjustment for age, AMI (OR 9.34, 95% CI 1.66-52.4) and BI (OR 35.6, 95% CI 3.41-370) were associated with death. Superior mesenteric artery stenosis of >70% had a clinically relevant association with BI (OR 5.23, 95% CI 1.43-19.13; p = .012)**.**
Conclusion: Age, symptomatic PAD, AMI, and BI were risk factors for death after elective OSR in women. The association between a >70% SMA stenosis and BI may call for action in selected cases.

Gepubliceerd: EJVES Vasc Forum. 2022;57:17-27.
Impact factor: 0 ; Q NVT

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44. The association between plate location and hardware removal following ulna shortening osteotomy: a cohort study
Teunissen JS, Al Shaer S, van der Heijden BPA, Selles RW, Hovius SER, Zöphel OT.

Hardware removal after ulna shortening osteotomy is common. We evaluated the association between plate location and hardware removal rate in 326 procedures in 321 patients with a median follow-up of 4.3 years (IQR 3.3) and corrected for confounding variables and did survival analyses. Complications were scored using the International Consortium for Health Outcome Measurement complications in Hand and Wrist Conditions tool. The 1-year and 5-year reoperation rates for hardware removal were 21% and 46% in the anterior group versus 37% and 64% in the dorsal group. Anterior plate placement was independently associated with a decreased immediate risk of hardware removal. Higher age, male sex and treatment on the dominant side were also associated with a reduced risk of hardware removal. We did not find a difference in hardware removal rates

between freehand or jig-guided ulna shortening osteotomies. We noted perioperative problems in 3% of the procedures and complications in 20%.Level of evidence: III.

Gepubliceerd: J Hand Surg Eur Vol. 2022;47(8):831-8.
Impact factor: 2.206 ; Q3

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45. Severity of oEsophageal Anastomotic Leak in patients after oesophagectomy: the SEAL score
Ubels S, Verstegen M, Klarenbeek B, Bouwense S, van Berge Henegouwen M, Daams F, van Det MJ, Griffiths EA, Haveman JW, Heisterkamp J, Koshy R, Nieuwenhuijzen G, Polat F, Siersema PD, Singh P, Wijnhoven B, Hannink G, van Workum F, Rosman C, TENTACLE—Esophagus Collaborative Group: Slootmans C, Steenvoorde P, Mastboom W.

Background: Anastomotic leak (AL) is a common but severe complication after oesophagectomy. It is unknown how to determine the severity of AL objectively at diagnosis. Determining leak severity may guide treatment decisions and improve future research. This study aimed to identify leak-related prognostic factors for mortality, and to develop a Severity of oEsophageal Anastomotic Leak (SEAL) score**.**
Methods: This international, retrospective cohort study in 71 centres worldwide included patients with AL after oesophagectomy between 2011 and 2019. The primary endpoint was 90-day mortality. Leak-related prognostic factors were identified after adjusting for confounders and were included in multivariable logistic regression to develop the SEAL score. Four classes of leak severity (mild, moderate, severe, and critical) were defined based on the risk of 90-day mortality, and the score was validated internally**.**
Results: Some 1509 patients with AL were included and the 90-day mortality rate was 11.7 per cent. Twelve leak-related prognostic factors were included in the SEAL score. The score showed good calibration and discrimination (c-index 0.77, 95 per cent c.i. 0.73 to 0.81). Higher classes of leak severity graded by the SEAL score were associated with a significant increase in duration of ICU stay, healing time, Comprehensive Complication Index score, and Esophagectomy Complications Consensus Group classification**.**
Conclusion: The SEAL score grades leak severity into four classes by combining 12 leak-related predictors and can be used to the assess severity of AL after oesophagectomy.

Gepubliceerd: Br J Surg. 2022;109(9):864-71.
Impact factor: 11.782; Q1

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46. Fluorescence angiography to assess intestinal viability during emergency laparoscopy for small bowel obstruction-A video vignette
Vaassen HGM, Sprakel J, Lips DJ.

Gepubliceerd: Colorectal Dis. 2022;24(11):1444-5.
Impact factor: 3.917; Q3

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47. Fluorescence-Based Quantification of Gastrointestinal Perfusion: A Step Towards an Automated Approach
Vaassen HGM, Wermelink B, Geelkerken RH, Lips DJ.

Background: Qualitative fluorescence angiography (FA) provides insights into intestinal tissue perfusion, but today it is not yet accurate in predicting anastomotic leakage. To improve peroperative

detection of impaired perfusion, quantified parameters should be investigated using a standardized method. The aim of this study was to develop a (semi)automated algorithm for comprehensive and convenient analysis of FA parameters.
Materials and Methods: An analysis tool was developed for the extraction of quantified FA parameters. The start- and endpoint of intensity increase (T(0) and Tmax) were automatically detected in the intensity-time curves. Algorithm performance was measured against manual assignment of T(0) and Tmax by 9 independent observers in 18 in vivo generated test signals, using the intraclass correlation coefficient (ICC). Characteristics of parameter T1⁄2 (time to 50% of maximal intensity) were analyzed in normally perfused small intestine of 32 subjects who underwent robotic laparoscopic surgery. Since ethical approval was not required under the Dutch law, the need for informed consent was waived.
Results: Automated detection of T(0) and Tmax was successful in all subjects. Output of the algorithm had an excellent agreement with the median of the human observations: ICC = 0.95 (95% confidence interval: 0.86-0.96). Overall, T1⁄2 had a median value of 5.1 (interquartile range = 2.4) seconds and a minimal and maximal value of 1.3 and 9.9 seconds, respectively.
Conclusions: The presented method provided convenient data analysis in the search for effective FA quantification. Future research should expand the data to find adequate threshold values for peroperatively identifying insufficient perfusion and investigate the influence of physiological conditions.

Gepubliceerd: J Laparoendosc Adv Surg Tech A. 2022;32(3):293-8.
Impact factor: 0.648 ; Q3

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48. Intraoperative quantification of fluorescence angiography for assessment of intestinal perfusion: in vivo exploration of clinical value
Vaassen HGM, Wermelink B, Manohar S, Geelkerken RH, Lips DJ.

Gepubliceerd: BJS Open. 2022;6(3).
Impact factor: 3.875 ; Q1

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49. The Effect of Arterial Disease Level on Outcomes of Supervised Exercise Therapy for Intermittent Claudication: A Prospective Cohort Study
van den Houten MML, Jansen S, van der Laan L, Vriens P, Willigendael EM, Koelemay MJW, Scheltinga MRM, Teijink JAW.

Objective: To assess whether level of arterial obstruction determines the effectiveness of SET in patients with IC.
Background data: Guidelines advocate SET before invasive treatment for IC, but early revascularization remains widespread, especially in patients with aortoiliac disease**.**
Methods: Patients were recruited from 10 Dutch centers between October 2017 and October 2018. Participants received SET first, followed by endovascular or open revascularization in case of insufficient effect. They were grouped according to level of stenosis (aortoiliac, femoropopliteal, multilevel, or rest group with no significant stenosis). Changes from baseline walking performance (maximal and functional walking distance on a treadmill test, 6-minute walk test) and vascular quality of life questionnaire-6 at 3 and 6 months were compared, after multivariate adjustment for possible confounders. Freedom from revascularization was estimated with Kaplan-Meier analysis**.**
Results: Some 267 patients were eligible for analysis (aortoiliac n = 70, 26%; femoropopliteal n = 115, 43%; multilevel n = 69, 26%; rest n = 13, 5%). No between group differences in walking performance or vascular quality of life questionnaire-6 were found. Mean improvement in maximal walking

distance after 6 months was 439 m [99% confidence interval (CI) 297-581], 466 m (99% CI 359-574), 353 m (99% CI 210-496), and 403 m (99% CI 58-749), respectively (P = 0.40). Freedom from intervention was 73.9% for aortoiliac disease and 88.6% for femoropopliteal disease (hazard ratio 2.46, 99% CI 0.96 - 6.30, P = 0.013).
Conclusions: Short-term effectiveness of SET for IC is not determined by the location of stenosis. Although aortoiliac disease patients improved walking performance and health-related quality of life similarly compared to other arterial disease level groups, they underwent revascularization more often.

Gepubliceerd: Ann Surg. 2022;275(3):609-16.
Impact factor: 13.787 ; Q1

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50. Evaluation of electrocardiogram-gated computed tomography angiography to quantify changes in geometry and dynamic behavior of the iliac artery after placement of the Gore Excluder Iliac Branch Endoprosthesis
van Helvert M, Simmering JA, Koenrades MA, Slump CH, Heyligers JM, Geelkerken RH, Reijnen MM.

Background: The GORE(®) EXCLUDER(®) Iliac Branch Endoprosthesis (IBE) is designed to treat iliac aneurysms with preservation of blood flow through the internal iliac artery (IIA). Little is known about the influence of IBE placement on the IIA geometry. This study aimed to provide detailed insights in the dynamic behavior and geometry of the common iliac artery (CIA) and IIA trajectory and how these are influenced after treatment with an IBE**.**
Methods: Pre- and postoperative electrocardiogram-gated computed tomography angiography (ECG-gated CTA) scans were acquired in a prospective study design and analyzed with in-house written algorithms designed for aorto-iliac and endoprosthesis deformation evaluation. Cardiac pulsatility-induced motion patterns and pathlengths were computed by tracking predefined locations on the aorto-iliac tract. Centerlines through the CIA-IIA trajectory were used to investigate the static and dynamic geometry, including curvature, torsion, length and Tortuosity Index (TI)**.**
Results: Fourteen CIA-IIA trajectories were analyzed before and after IBE placement. Cardiac pulsatility-induced motion and pathlengths increased after IBE placement, especially at mid IIA and the first IIA bifurcation (P≤0.04). After IBE placement, static and dynamic curvature, length and TI decreased significantly (P<0.05). Furthermore, the average dynamic torsion increased significantly (P=0.030). The remaining geometrical outcomes were not statistically significant.
Conclusions: The placement of an IBE device stiffens and straightens the CIA-IIA trajectory. Its relation with clinical outcome is yet to be investigated, which can be done thoroughly with the ECG-gated CTA algorithms used in this study.

Gepubliceerd: J Cardiovasc Surg (Torino). 2022;63(4):454-63.
Impact factor: 0 ; Q NVT

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51. Prognostic factors for mortality in 123 severe cases of necrotizing fasciitis in 5 hospitals in the Netherlands between 2003 and 2017
van Stigt S, Knubben M, Schrooten T, Tan E.

Purpose: Necrotizing fasciitis (NF) is a severe soft tissue infection with a high morbidity and mortality. With early diagnosis and treatment this could be reduced. Unfortunately, the diagnosis of necrotizing fasciitis can be very difficult. In recent years many risk factors have been identified. In 2004, the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was developed. A tool that could help diagnosing NF. In this study, we search for prognostic factors for mortality in necrotizing fasciitis**.**

Methods: All adult patients with histopathological or surgical confirmed NF needed to be admitted to the intensive care unit for at least 24 h between January 2003 and December 2017 in five hospitals from the Nijmegen teaching region were included. We excluded patients with other forms of soft tissue infections or patients with an intensive care unit (ICU) stay of < 24 h because we exclusively wanted to include patients with a fulminant course of necrotizing fasciitis**.**
Results: We have included 123 cases. The overall mortality was 31.7% (N = 39). The overall mean LRINEC score was 7.4 ± 2.7. Patients who died as the result of NF had a significantly higher median LRINEC score (8 vs. 7, p = 0.034). Other parameters found to be associated with mortality are age ≥ 60 years, cardiovascular disease in the medical history, ≥ 2 comorbidities, and lactate level greater than 1.7 mmol/L**.**
Conclusion: LRINEC score should be calculated in all patients presenting with NF to provide an additional source for clinical outcome. A high LRINEC score could implicate a higher risk of mortality. Especially in elderly patients, with a cardiac history, more than two comorbidities or a lactate level greater than 1.7 mmol/L.

Gepubliceerd: Eur J Trauma Emerg Surg. 2022;48(2):1189-95.
Impact factor: 2.374 ; Q3

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52. Impact of severe necrotizing fasciitis on quality of life in the Netherlands
van Stigt SFL, Schrooten TKJ, Knubben M, Tan E.

Purpose: Necrotizing fasciitis (NF) is a severe soft-tissue infection which can leave survivors with big and multiple disfiguring alterations to their bodies, which can negatively affect the lives of patients by causing functional limitations and altered self-perception. In this study we aim to find if NF affect (self-reported) quality of life (QoL) in patients surviving NF**.**
Methods: All patients with (histopathological or surgical confirmed) NF who were admitted to the intensive care unit for 24 h or more between January 2003 and December 2017 in five hospitals from the Nijmegen teaching region were included. Quality of life was measured with the SF-36 and WHOQol-BREF. These results were compared to reference populations from the Netherlands and a Australian reference population**.**
Results: 44 out of 60 patients (73.3%) who were contacted returned the surveys and were eligible for analysis. These patients showed lowered levels of quality of life on multiple domains of the SF-36: physical functioning, role limitations due to physical health, vitality and general health. The physical domain of the WHOQol-BREF showed also significant lowered levels of quality of life**.**
Conclusion: NF is a severe illness with a high morbidity and mortality rate. This study shows that patients who do survive NF have decreased (self-reported) quality of life in multiple domains with a focus on decreased physical functioning. During and after admission realistic expectations should be discussed and there should be more attention to signs of permanent disability. That way extra support by a physiotherapist or social worker can be provided.

Gepubliceerd: Eur J Trauma Emerg Surg. 2022;48(6):4805-11.
Impact factor: 2.374 ; Q3

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53. Bihormonal Artificial Pancreas With Closed-Loop Glucose Control vs Current Diabetes Care After Total Pancreatectomy: A Randomized Clinical Trial
van Veldhuisen CL, Latenstein AEJ, Blauw H, Vlaskamp LB, Klaassen M, Lips DJ, Bonsing BA, van der Harst E, Stommel MWJ, Bruno MJ, van Santvoort HC, van Eijck CHJ, van Dieren S, Busch OR, Besselink MG, DeVries JH.

Importance: Glucose control in patients after total pancreatectomy is problematic because of the complete absence of α- and β-cells, leading to impaired quality of life. A novel, bihormonal artificial pancreas (BIHAP), using both insulin and glucagon, may improve glucose control, but studies in this setting are lacking.
Objective: To assess the efficacy and safety of the BIHAP in patients after total pancreatectomy.
Design, Setting and participants: This randomized crossover clinical trial compared the fully closed-loop BIHAP with current diabetes care (ie, insulin pump or pen therapy) in 12 adult outpatients after total pancreatectomy. Patients were recruited between August 21 and November 16, 2020. This first-in-patient study began with a feasibility phase in 2 patients. Subsequently, 12 patients were randomly assigned to 7-day treatment with the BIHAP (preceded by a 5-day training period) followed by 7-day treatment with current diabetes care, or the same treatments in reverse order. Statistical analysis was by Wilcoxon signed rank and Mann-Whitney U tests, with significance set at a 2-sided P < .05.
Main Outcomes and Measures: The primary outcome was the percentage of time spent in euglycemia (70-180 mg/dL [3.9-10 mmol/L]) as assessed by continuous glucose monitoring**.**
Results: In total, 12 patients (7 men and 3 women; median [IQR] age, 62.5 [43.1-74.0] years) were randomly assigned, of whom 3 did not complete the BIHAP phase and 1 was replaced. The time spent in euglycemia was significantly higher during treatment with the BIHAP (median, 78.30%; IQR, 71.05%-82.61%) than current diabetes care (median, 57.38%; IQR, 52.38%-81.35%; P = .03). In addition, the time spent in hypoglycemia (<70 mg/dL [3.9 mmol/L]) was lower with the BIHAP (median, 0.00% [IQR, 0.00%-0.07%] vs 1.61% [IQR, 0.80%-3.81%]; P = .004). No serious adverse events occurred.
Conclusions and Relevance: Patients using the BIHAP after total pancreatectomy experienced an increased percentage of time in euglycemia and a reduced percentage of time in hypoglycemia compared with current diabetes care, without apparent safety risks. Larger randomized trials, including longer periods of treatment and an assessment of quality of life, should confirm these findings.
Trial registration: trialregister.nl Identifier: NL8871.

Gepubliceerd: JAMA Surg. 2022;157(10):950-7.
Impact factor: 16.685 ; Q1

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54. Improved preoperative aerobic fitness following a home-based bimodal prehabilitation programme in high-risk patients scheduled for liver or pancreatic resection
van Wijk L, Bongers BC, Berkel AEM, Buis CI, Reudink M, Liem MSL, Slooter GD, van Meeteren NLU, Klaase JM.

Gepubliceerd: Br J Surg. 2022;109(11):1036-9.
Impact factor: 11.782; Q1

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55. Internal Jugular Vein Geometry Under Multiple Inclination Angles with 3D Low-Field MRI in Healthy Volunteers
van Zandwijk JK, Kuijer KM, Stassen CM, Ten Haken B, Simonis FFJ.

Background: Cerebral venous pathways are subjected to geometrical and patency changes due to body position. The internal jugular veins (IJVs) are the main venous drainage pathway in supine position. Their patency and geometry should be evaluated under different body inclination angles over a three-dimensional (3D) volume in the healthy situation to better understand pathological cases.

Purpose: To investigate whether positional changes in the body can affect the geometrical properties and patency of the venous system.
Study type: Prospective.
Population: 15 healthy volunteers, of which seven males and median age 22 years in a range of 19-59.
Field strength/sequence: A 0.25-T tiltable MRI system was used to scan volunteers in 90° (sitting position), 69°, 45°, 21°, and 0° (supine position) in the transverse plane with the top at vertebra C2. A gradient echo sequence was used.
Assessment: Three observers assessed IJVs on patency and created automatic centerlines from which diameter and patency were analysed perpendicular to the vessel at every 4 mm starting at the level of C2.
Statistical tests: A Student's t test was used to find statistical difference ($p < 0.05$) in average IJV diameters per inclination angle**.**
Results: The amount of fully collapsed IJVs increased from 33% to 93% (left IJV) and 14% to 80% (right IJV) when increasing the inclination angle from 0° to 90°. In both IJVs, the mean diameter (±SD) of the open vessels was significantly higher at 0° than 90° with 6.3 ± 0.5 mm vs. 4.4 ± 0.1 mm (left IJV) and 6.6 ± 0.6 mm vs. 4.3 ± 0.4 mm (right IJV).
Data conclusion: Tiltable low-field MRI can be used to assess IJV geometry and its associated venous pathways in 3D under multiple inclination angles. Next to a higher amount of collapsed vessels, the average diameter of noncollapsed vessels decreases with increasing inclination angles for both left and right IJVs.
Level of evidence: 2
Technical efficacy stage: 1.

Gepubliceerd: J Magn Reson Imaging. 2022;56(5):1302-8.
Impact factor: 5.119 ; Q1

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56. Prophylactic abdominal drainage or no drainage after distal pancreatectomy (PANDORINA): a binational multicenter randomized controlled trial
Vissers FL, Balduzzi A, van Bodegraven EA, van Hilst J, Festen S, Hilal MA, Asbun HJ, Mieog JSD, Koerkamp BG, Busch OR, Daams F, Luyer M, De Pastena M, Malleo G, Marchegiani G, Klaase J, Molenaar IQ, Salvia R, van Santvoort HC, Stommel M, Lips D, Coolsen M, Bassi C, van Eijck C, Besselink MG.

Background: Prophylactic abdominal drainage is current standard practice after distal pancreatectomy (DP), with the aim to divert pancreatic fluid in case of a postoperative pancreatic fistula (POPF) aimed to prevent further complications as bleeding. Whereas POPF after pancreatoduodenectomy, by definition, involves infection due to anastomotic dehiscence, a POPF after DP is essentially sterile since the bowel is not opened and no anastomoses are created. Routine drainage after DP could potentially be omitted and this could even be beneficial because of the hypothetical prevention of drain-induced infections (Fisher, Surgery 52:205-22, 2018). Abdominal drainage, moreover, should only be performed if it provides additional safety or comfort to the patient. In clinical practice, drains cause clear discomfort. One multicenter randomized controlled trial confirmed the safety of omitting abdominal drainage but did not stratify patients according to their risk of POPF and did not describe a standardized strategy for pancreatic transection. Therefore, a large pragmatic multicenter randomized controlled trial is required, with prespecified POPF risk groups and a homogeneous method of stump closure. The objective of the PANDORINA trial is to evaluate the non-inferiority of omitting routine intra-abdominal drainage after DP on postoperative morbidity (Clavien-Dindo score ≥ 3), and, secondarily, POPF grade B/C.

Methods/Design: Binational multicenter randomized controlled non-inferiority trial, stratifying patients to high and low risk for POPF grade B/C and incorporating a standardized strategy for pancreatic transection. Two groups of 141 patients (282 in total) undergoing elective DP (either open or minimally invasive, with or without splenectomy). Primary outcome is postoperative rate of morbidity (Clavien-Dindo score ≥ 3), and the most relevant secondary outcome is grade B/C POPF. Other secondary outcomes include surgical reintervention, percutaneous catheter drainage, endoscopic catheter drainage, abdominal collections (not requiring drainage), wound infection, delayed gastric emptying, postpancreatectomy hemorrhage as defined by the international study group for pancreatic surgery (ISGPS) (Wente et al., Surgery 142:20-5, 2007), length of stay (LOS), readmission within 90 days, in-hospital mortality, and 90-day mortality.
Discussion: PANDORINA is the first binational, multicenter, randomized controlled non-inferiority trial with the primary objective to evaluate the hypothesis that omitting prophylactic abdominal drainage after DP does not worsen the risk of postoperative severe complications (Wente etal., Surgery 142:20-5, 2007; Bassi et al., Surgery 161:584-91, 2017). Most of the published studies on drain placement after pancreatectomy focus on both pancreatoduodenectomy and DP, but these two entities present are associated with different complications and therefore deserve separate evaluation (McMillan et al., Surgery 159:1013-22, 2016; Pratt et al., J Gastrointest Surg 10:1264-78, 2006). The PANDORINA trial is innovative since it takes the preoperative risk on POPF into account based on the D-FRS and it warrants homogenous stump closing by using the same graded compression technique and same stapling device (de Pastena et al., Ann Surg 2022; Asbun and Stauffer, Surg Endosc 25:2643-9, 2011).

Gepubliceerd: Trials. 2022;23(1):809.
Impact factor: 2.728 ; Q4

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57. Missed injuries in trauma patients: the value of a diagnostic thoracotomy or thoracoscopy during surgical stabilisation of rib fractures
Wemeijer TM, Hogeboom W, Steenvoorde P, Withaar DS, de Groot R.

Purpose: Over the last decade Surgical Stabilisation of Rib Fractures (SSFR) gained popularity in our hospital. With increased numbers, we noted that frequently injuries were missed during primary/secondary survey and radiological imaging that were found during the surgical procedure. With this observation, the research question was formulated: What is the value of diagnostics thoracotomy or thoracoscopy during surgical stabilisation of rib fractures?
Methods: In a single-centre, retrospective study between February 2010 and December 2019, trauma patients who underwent Surgical Stabilisation of Rib Fractures (SSFR) and an inspection thoracotomy were included. All radiological injuries were compared with intraoperative findings. Missed injuries that were discovered during the surgical procedure that were not analysed during primary/secondary survey or on radiological imaging were recorded and retrospectively analysed by an independent radiologist**.**
Results: Fifty-one patients were included. Eight patients had additional injuries; all had a diaphragmatic rupture, one patient had an additional stomach laceration, and another patient had a significant lung laceration in need of surgical repair. On a CT scan there are 7 signs of predictive value for a diaphragmatic rupture. Only 13 out of the total of 56 diaphragm rupture CT signs were confirmed on the primary CT scans of the eight patients with diaphragmatic injuries; therefore, still 77% of signs could not be confirmed by initial radiological findings**.**
Conclusion: With the recent shift towards surgical stabilisation of rib fractures, an inspection thoracoscopy or thoracotomy during SSFR should be considered to minimise the incidence of missed intrathoracic injuries requiring early or late surgical treatment.

Gepubliceerd: Ir J Med Sci. 2022;191(3):1285-9.
Impact factor: 2.089 ; Q3

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58. Assessing the Microcirculation of the Foot with Laser Speckle Contrast Imaging During Endovascular and Hybrid Revascularisation Procedures in Patients with Chronic Limb Threatening Ischaemia
Wermelink B, Mennes OA, Van Baal JG, Steenbergen W, Geelkerken RH, Study group includes: Aarnink SH; Beuk R; Brusse-Keiser M; Haalboom M; Meerwaldt R; Willigendael EM.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2022;63(6):898-9.
Impact factor: 6.427 ; Q1

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59. Interobserver Variability in CT-based Morphologic Tumor Response Assessment of Colorectal Liver Metastases
Wesdorp NJ, Kemna R, Bolhuis K, van Waesberghe J, Nota I, Struik F, Oulad Abdennabi I, Phoa S, van Dieren S, van Amerongen MJ, Chapelle T, Dejong CHC, Engelbrecht MRW, Gerhards MF, Grünhagen D, van Gulik TM, Hermans JJ, de Jong KP, Klaase JM, Liem MSL, van Lienden KP, Molenaar IQ, Patijn GA, Rijken AM, Ruers TM, Verhoef C, de Wilt JHW, Swijnenburg RJ, Punt CJA, Huiskens J, Stoker J, Kazemier G.

Purpose: To evaluate interobserver variability in the morphologic tumor response assessment of colorectal liver metastases (CRLM) managed with systemic therapy and to assess the relation of morphologic response with gene mutation status, targeted therapy, and Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 measurements.
Materials and Methods: Participants with initially unresectable CRLM receiving different systemic therapy regimens from the randomized, controlled CAIRO5 trial (NCT02162563) were included in this prospective imaging study. Three radiologists independently assessed morphologic tumor response on baseline and first follow-up CT scans according to previously published criteria. Two additional radiologists evaluated disagreement cases. Interobserver agreement was calculated by using Fleiss κ. On the basis of the majority of individual radiologic assessments, the final morphologic tumor response was determined. Finally, the relation of morphologic tumor response and clinical prognostic parameters was assessed.
Results: In total, 153 participants (median age, 63 years [IQR, 56-71]; 101 men) with 306 CT scans comprising 2192 CRLM were included. Morphologic assessment performed by the three radiologists yielded 86 (56%) agreement cases and 67 (44%) disagreement cases (including four major disagreement cases). Overall interobserver agreement between the panel radiologists on morphology groups and morphologic response categories was moderate (κ = 0.53, 95% CI: 0.48, 0.58 and κ = 0.54, 95% CI: 0.47, 0.60). Optimal morphologic response was particularly observed in patients treated with bevacizumab (P = .001) and in patients with RAS/BRAF mutation (P = .04). No evidence of a relationship between RECIST 1.1 and morphologic response was found (P = .61).
Conclusion: Morphologic tumor response assessment following systemic therapy in participants with CRLM demonstrated considerable interobserver variability.
Clinical trial registration no. NCT02162563 Supplemental material is available for this article. © RSNA, 2022.

Gepubliceerd: Radiol Imaging Cancer. 2022;4(3):e210105.
Impact factor: 0 ; Q NVT

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60. Adhesion formation after surgery for locally advanced colonic cancer in the COLOPEC trial
Zwanenburg ES, Wisselink DD, Klaver CEL, Brandt ARM, Bremers AJA, Burger JWA, van Grevenstein WMU, Hemmer PHJ, de Hingh I, Kok NFM, Wiezer MJ, Tuynman JB, Tanis PJ, COLOPEC trial collaborators: van Duyn EB.

Gepubliceerd: Br J Surg. 2022;109(4):315-8.
Impact factor: 11.782; Q1

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61. The measured distance between tumor cells and the peritoneal surface predicts the risk of peritoneal metastases and offers an objective means to differentiate between pT3 and pT4a colon cancer
Zwanenburg ES, Wisselink DD, Klaver CEL, van der Bilt JDW, Tanis PJ, Snaebjornsson P, COLOPEC trial collaborators: van Duyn EB.

Substantial variability exists in what pathologists consider as pT4a in colorectal cancer when tumor cells are within 1 mm of the free peritoneal surface. This study aimed to determine if the measured sub-millimeter distance between tumor cells and the free peritoneal surface would offer an objective means of stratifying patients according to the risk of developing peritoneal metastases. Histological slides of patients included in the COLOPEC trial, with resectable primary c/pT4N0-2M0 colon cancer, were centrally reassessed. Specific tumor morphological variables were collected, including distance from tumor to free peritoneal surface, measured in micrometers (µm). The primary outcome, 3-year peritoneal metastasis rate, was compared between four groups of patients stratified for relation of tumor cells to the peritoneum: 1) Full peritoneal penetration with tumor cells on the peritoneal surface, 2) 0-99 µm distance to the peritoneum, 3) 100-999 µm to the peritoneum, and 4) ≥1000 µm to the peritoneum, by using Kaplan-Meier analysis. In total, 189 cases were included in the present analysis. Cases with full peritoneal penetration (n = 89), 0-99 µm distance to the peritoneal surface (n = 34), 100-999 µm distance (n = 33), and ≥1000 µm distance (n = 33), showed significantly different 3-year peritoneal metastases rates of 25% vs 29% vs 6% vs 12%, respectively (Log Rank, p = 0.044). N-category did not influence the risk of peritoneal metastases in patients with a tumor distance beyond 100 µm, while only the N2 category seemed to result in an additive risk in patients with a distance of 0-99 µm. The findings of this study suggest that the measured shortest distance between tumor cells and the free peritoneal surface is useful as an objective means of stratifying patients according to the risk of developing peritoneal metastases. This simple measurement is practical and may help in providing a precise definition of pT4a.
Trial registration: NCT02231086 (Clinicaltrials.gov).

Gepubliceerd: Mod Pathol. 2022;35(12):1991-2001.
Impact factor: 8.209 ; Q1

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62. Performance with robotic surgery versus 3D- and 2D-laparoscopy during pancreatic and biliary anastomoses in a biotissue model: pooled analysis of two randomized trials
Zwart MJW, Jones LR, Fuente I, Balduzzi A, Takagi K, Novak S, Stibbe LA, de Rooij T, van Hilst J, van Rijssen LB, van Dieren S, Vanlander A, van den Boezem PB, Daams F, Mieog JSD, Bonsing BA, Rosman C, Festen S, Luyer MD, Lips DJ, Moser AJ, Busch OR, Abu Hilal M, Hogg ME, Stommel MWJ, Besselink MG.

Background: Robotic surgery may improve surgical performance during minimally invasive pancreatoduodenectomy as compared to 3D- and 2D-laparoscopy but comparative studies are lacking. This study assessed the impact of robotic surgery versus 3D- and 2D-laparoscopy on surgical

performance and operative time using a standardized biotissue model for pancreatico- and hepatico-jejunostomy using pooled data from two randomized controlled crossover trials (RCTs)**.**
Methods: Pooled analysis of data from two RCTs with 60 participants (36 surgeons, 24 residents) from 11 countries (December 2017-July 2019) was conducted. Each included participant completed two pancreatico- and two hepatico-jejunostomies in biotissue using 3D-robotic surgery, 3D-laparoscopy, or 2D-laparoscopy. Primary outcomes were the objective structured assessment of technical skills (OSATS: 12-60) rating, scored by observers blinded for 3D/2D and the operative time required to complete both anastomoses. Sensitivity analysis excluded participants with excess experience compared to others**.**
Results: A total of 220 anastomoses were completed (robotic 80, 3D-laparoscopy 70, 2D-laparoscopy 70). Participants in the robotic group had less surgical experience [median 1 (0-2) versus 6 years (4-12), $p < 0.001$], as compared to the laparoscopic group. Robotic surgery resulted in higher OSATS ratings (50, 43, 39 points, $p = .021$ and $p < .001$) and shorter operative time (56.5, 65.0, 81.5 min, $p = .055$ and $p < .001$), as compared to 3D- and 2D-laparoscopy, respectively, which remained in the sensitivity analysis**.**
Conclusion: In a pooled analysis of two RCTs in a biotissue model, robotic surgery resulted in better surgical performance scores and shorter operative time for biotissue pancreatic and biliary anastomoses, as compared to 3D- and 2D-laparoscopy.

Gepubliceerd: Surg Endosc. 2022;36(6):4518-28.
Impact factor: 3.452 ; Q2

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63. Outcomes of a Multicenter Training Program in Robotic Pancreatoduodenectomy (LAELAPS-3)
Zwart MJW, Nota CLM, de Rooij T, van Hilst J, Te Riele WW, van Santvoort HC, Hagendoorn J, Borei Rinkes IHM, van Dam JL, Latenstein AEJ, Takagi K, Tran KTC, Schreinemakers J, van der Schelling GP, Wijsman JH, Festen S, Daams F, Luyer MD, de Hingh I, Mieog JSD, Bonsing BA, Lips DJ, Hilal MA, Busch OR, Saint-Marc O, Zehl HJ, 2nd, Zureikat AH, Hogg ME, Molenaar IQ, Besselink MG, Koerkamp BG.

Objective: To assess feasibility and safety of a multicenter training program in robotic pancreatoduodenectomy (RPD) adhering to the IDEAL framework for implementation of surgical innovation.
Background: Good results for RPD have been reported from single center studies. However, data on feasibility and safety of implementation through a multicenter training program in RPD are lacking**.**
Methods: A multicenter training program in RPD was designed together with the University of Pittsburgh Medical Center, including an online video bank, robot simulation exercises, biotissue drills, and on-site proctoring. Benchmark patients were based on the criteria of Clavien. Outcomes were collected prospectively (March 2016-October 2019). Cumulative sum analysis of operative time was performed to distinguish the first and second phase of the learning curve. Outcomes were compared between both phases of the learning curve. Trends in nationwide use of robotic and laparoscopic PD were assessed in the Dutch Pancreatic Cancer Audit**.**
Results: Overall, 275 RPD procedures were performed in seven centers by 15 trained surgeons. The recent benchmark criteria for low-risk PD were met by 125 (45.5%) patients. The conversion rate was 6.5% (n = 18) and median blood loss 250ml [interquartile range (IQR) 150-500]. The rate of Clavien-Dindo grade ≥III complications was 44.4% (n = 122), postoperative pancreatic fistula (grade B/C) rate 23.6% (n = 65), 90-day complication-related mortality 2.5% (n = 7) and 90-day cancer-related mortality 2.2.% (n = 6). Median postoperative hospital stay was 12 days (IQR 8-20). In the subgroup of patients with pancreatic cancer (n = 80), the major complication rate was 31.3% and POPF rate was 10%. Cumulative sum analysis for operative time found a learning curve inflection point at 22 RPDs (IQR 10-35) with similar rates of Clavien-Dindo grade ≥III complications in the first and second

phase (43.4% vs 43.8%, P = 0.956, respectively). During the study period the nationwide use of laparoscopic PD reduced from 15% to 1%, whereas the use of RPD increased from 0% to 25%. **Conclusions:** This multicenter RPD training program in centers with sufficient surgical volume was found to be feasible without a negative impact of the learning curve on clinical outcomes.

Gepubliceerd: Ann Surg. 2022;276(6):e886-e95.
Impact factor: 13.787 ; Q1

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64. A Comprehensive Grading System for a Magnetic Sentinel Lymph Node Biopsy Procedure in Head and Neck Cancer Patients
Nieuwenhuis ER, Kolenaar B, Hof JJ, van Baarlen J, van Bemmel AJM, Christenhusz A, Scheenen TWJ, Ten Haken B, de Bree R, Alic L.

A magnetic sentinel lymph node biopsy ((SLN)B) procedure has recently been shown feasible in oral cancer patients. However, a grading system is absent for proper identification and classification, and thus for clinical reporting. Based on data from eight complete magnetic SLNB procedures, we propose a provisional grading system. This grading system includes: (1) a qualitative five-point grading scale for MRI evaluation to describe iron uptake by LNs; (2) an ex vivo count of resected SLN with a magnetic probe to quantify iron amount; and (3) a qualitative five-point grading scale for histopathologic examination of excised magnetic SLNs. Most SLNs with iron uptake were identified and detected in level II. In this level, most variance in grading was seen for MRI and histopathology; MRI and medullar sinus were especially highly graded, and cortical sinus was mainly low graded. On average 82 ± 58 µg iron accumulated in harvested SLNs, and there were no significant differences in injected tracer dose (22.4 mg or 11.2 mg iron). In conclusion, a first step was taken in defining a comprehensive grading system to gain more insight into the lymphatic draining system during a magnetic SLNB procedure.

Gepubliceerd: Cancers (Basel). 2022;14(3).
Impact factor: 6.575; Q1

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65. Recurrent Disease After Esophageal Cancer Surgery: A Substudy of The Dutch Nationwide Ivory Study
Kalff MC, Henckens SPG, Voeten DM, Heineman DJ, Hulshof MCCM, van Laarhoven HWM, Eshuis WJ, Baas PC, Bahadoer RR, Belt EJT, Brattinga B, Claassen L, Ćosović A, Crull D, Daams F, van Dalsen AD, Dekker JWT, van Det MJ, Drost M, van Duijvendijk P, van Esser S, Gaspersz MP, Görgec B, Groenendijk RPR, Hartgrink HH, van der Harst E, Haveman JW, Heisterkamp J, van Hillegersberg R, Kelder W, Kingma BF, Koemans WJ, Kouwenhove EA, Lagarde SM, Lecot F, van der Linden PP, Luyer MDP, Nieuwenhuijzen GAP, Olthof PB, van der Peet DL, Pierie JEN, Pierik EGJMR, Plat VD, Polat F, Rosman C, Ruurda JP, van Sandick JW, Scheer R, Slootmans CAM, Sosef MN, Sosef OV, de Steur WO, Stockmann HBAC, Stoop FJ, Vugts G, Vijgen GHEJ, Weeda VB, Wiezer MJ, van Oijen MGH, van Berge Henegouwen MI, Gisbertz SS.

Objective: This study investigated the patterns, predictors, and survival of recurrent disease following esophageal cancer surgery.
Background: Survival of recurrent esophageal cancer is usually poor, with limited prospects of remission.
Methods: This nationwide cohort study included patients with distal esophageal and gastroesophageal junction adenocarcinoma and squamous cell carcinoma after curatively intended

esophagectomy in 2007 to 2016 (follow-up until January 2020). Patients with distant metastases detected during surgery were excluded. Univariable and multivariable logistic regression were used to identify predictors of recurrent disease. Multivariable Cox regression was used to determine the association of recurrence site and treatment intent with postrecurrence survival.
Results: Among 4626 patients, 45.1% developed recurrent disease a median of 11 months postoperative, of whom most had solely distant metastases (59.8%). Disease recurrences were most frequently hepatic (26.2%) or pulmonary (25.1%). Factors significantly associated with disease recurrence included young age (≤65 y), male sex, adenocarcinoma, open surgery, transthoracic esophagectomy, nonradical resection, higher T-stage, and tumor positive lymph nodes. Overall, median postrecurrence survival was 4 months [95% confidence interval (95% CI): 3.6-4.4]. After curatively intended recurrence treatment, median survival was 20 months (95% CI: 16.4-23.7). Survival was more favorable after locoregional compared with distant recurrence (hazard ratio: 0.74, 95% CI: 0.65-0.84).
Conclusions: This study provides important prognostic information assisting in the surveillance and counseling of patients after curatively intended esophageal cancer surgery. Nearly half the patients developed recurrent disease, with limited prospects of survival. The risk of recurrence was higher in patients with a higher tumor stage, nonradical resection and positive lymph node harvest.

Gepubliceerd; Ann Surg. 2022;276(5):806-813
Impact factor: 9.00 ; Q1

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66. A nationwide assessment of hepatocellular adenoma resection: Indications and pathological discordance.

Haring MPD, Elfrink AKE, Oudmaijer CAJ, Andel PCM, Furumaya A, de Jong N, Willems CJJM, Huits T, Sijmons JML, Belt EJT, Bosscha K, Consten ECJ, Coolsen MME, van Duijvendijk P, Erdmann JI, Gobardhan P, de Haas RJ, van Heek T, Lam HD, Leclercq WKG, Liem MSL, Marsman HA, Patijn GA, Terkivatan T, Zonderhuis BM, Molenaar IQ, Te Riele WW, Hagendoorn J, Schaapherder AFM, IJzermans JNM, Buis CI, Klaase JM, de Jong KP, de Meijer VE, Dutch Benign Liver Tumor Group.

Hepatocellular adenomas (HCAs) are benign liver tumors associated with bleeding or malignant transformation. Data on the indication for surgery are scarce. We analyzed indications and outcome of patients operated for HCAs < 50 mm compared to HCAs ≥ 50 mm. Changes in final postoperative diagnosis were assessed. We performed a retrospective study that included patients who underwent resection for (suspected) HCAs in the Netherlands from 2014 to 2019. Indication for resection was analyzed and stratified for small (<50 mm) and large (≥50 mm) tumors. Logistic regression analysis was performed on factors influencing change in tumor diagnosis. Out of 222 patients who underwent surgery, 44 (20%) patients had a tumor <50 mm. Median age was 46 (interquartile range [IQR], 33-56) years in patients with small tumors and 37 (IQR, 31-46) years in patients with large tumors (p = 0.016). Patients with small tumors were more frequently men (21% vs. 5%, p = 0.002). Main indications for resection in patients with small tumors were suspicion of (pre)malignancy (55%), (previous) bleeding (14%), and male sex (11%). Patients with large tumors received operations because of tumor size >50 mm (52%), suspicion of (pre)malignancy (28%), and (previous) bleeding (5.1%). No difference was observed in HCA-subtype distribution between small and large tumors. Ninety-six (43%) patients had a postoperative change in diagnosis. Independent risk factors for change in diagnosis were tumor size <50 mm (adjusted odds ratio [aOR], 3.4; p < 0.01), male sex (aOR, 3.7; p = 0.03), and lack of hepatobiliary contrast-enhanced magnetic resonance imaging (CE-MRI) (aOR, 1.8; p = 0.04). Resection for small (suspected) HCAs was mainly indicated by suspicion of (pre)malignancy, whereas for large (suspected) HCAs, tumor size was the most prevalent indication. Male sex, tumor size <50 mm, and lack of hepatobiliary CE-MRI were independent risk factors for postoperative change in tumor diagnosis.

Gepubliceerd: Hepatol Commun. 2022;7(1):e2110.
Impact factor: 5.10; Q2

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67. Impact of the COVID-19 pandemic on surgical care in the Netherlands
de Graaff MR, Hogenbirk RNM, Janssen YF, Elfrink AKE, Liem RSL, Nienhuijs SW, de Vries JPM, Elshof JW, Verdaasdonk E, Melenhorst J, van Westreenen HL, Besselink MGH, Ruurda JP, van Berge Henegouwen MI, Klaase JM, den Dulk M, van Heijl M, Hegeman JH, Braun J, Voeten DM, Wurdemann FS, Warps AK, Alberga AJ, Suurmeijer JA, Akpinar EO, Wolfhagen N, van den Boom AL, Bolster-van Eenennaam MJ, van Duijvendijk P, Heineman DJ, Wouters M, Kruijff S, Dutch CovidSurg Collaborative Study Group: van Duyn EB, Geelkerken RH, de Groot R, Moekotte NL, Stam A, Voshaar A, Halfwerk F.

Background: The COVID-19 pandemic caused disruption of regular healthcare leading to reduced hospital attendances, repurposing of surgical facilities, and cancellation of cancer screening programmes. This study aimed to determine the impact of COVID-19 on surgical care in the Netherlands.
Methods: A nationwide study was conducted in collaboration with the Dutch Institute for Clinical Auditing. Eight surgical audits were expanded with items regarding alterations in scheduling and treatment plans. Data on procedures performed in 2020 were compared with those from a historical cohort (2018-2019). Endpoints included total numbers of procedures performed and altered treatment plans. Secondary endpoints included complication, readmission, and mortality rates.
Results: Some 12 154 procedures were performed in participating hospitals in 2020, representing a decrease of 13.6 per cent compared with 2018-2019. The largest reduction (29.2 per cent) was for non-cancer procedures during the first COVID-19 wave. Surgical treatment was postponed for 9.6 per cent of patients. Alterations in surgical treatment plans were observed in 1.7 per cent. Time from diagnosis to surgery decreased (to 28 days in 2020, from 34 days in 2019 and 36 days in 2018; $P < 0.001$). For cancer-related procedures, duration of hospital stay decreased (5 versus 6 days; $P < 0.001$). Audit-specific complications, readmission, and mortality rates were unchanged, but ICU admissions decreased (16.5 versus 16.8 per cent; $P < 0.001$).
Conclusion: The reduction in the number of surgical operations was greatest for those without cancer. Where surgery was undertaken, it appeared to be delivered safely, with similar complication and mortality rates, fewer admissions to ICU, and a shorter hospital stay.
COVID-19 has had a significant impact on healthcare worldwide. Hospital visits were reduced, operating facilities were used for COVID-19 care, and cancer screening programmes were cancelled. This study describes the impact of the COVID-19 pandemic on Dutch surgical healthcare in 2020. Patterns of care in terms of changed or delayed treatment are described for patients who had surgery in 2020, compared with those who had surgery in 2018-2019. The study found that mainly non-cancer surgical treatments were cancelled during months with high COVID-19 rates. Outcomes for patients undergoing surgery were similar but with fewer ICU admissions and shorter hospital stay. These data provide no insight into the burden endured by patients who had postponed or cancelled operations.

Gepubliceerd: Br J Surg. 2022;109(12):1282-92.
Impact factor: 11.782; Q1

Totale impact factor: 560.615
Gemiddelde impact factor: 8.367

Aantal artikelen 1e, 2e of laatste auteur: 18

Totale impact factor: 84.661
Gemiddelde impact factor: 4.703

Intensive care

1. Routine reporting of grey-white matter differentiation in early brain computed tomography in comatose patients after cardiac arrest: A substudy of the COACT trial
Adriaansens KO, Jewbali LSD, Lemkes JS, Spoormans EM, Meuwissen M, Blans MJ, van der Harst P, Eikemans BJW, Bleeker GB, Beishuizen A, Henriques JP, van der Lugt A, van Royen N, den Uil CA.

Aim: A multimodal approach is advised for neurological prognostication in comatose patients after out-of-hospital cardiac arrest (OHCA). Grey-white matter differentiation (grey-white ratio, GWR) obtained from a brain CT scan performed < 24 hours after return of circulation can be part of this approach. The aims of this study were to investigate the frequency and method of reporting the GWR in brain CT scan reports and their association with outcome**.**
Methods: This is a post-hoc descriptive analysis of the COACT trial. The primary endpoint was the reporting of GWR by the radiologist. Secondary endpoints were APACHE IV score, Cerebral Performance Categories at discharge and 90-day follow-up, Glasgow Coma Scale at discharge, GWR-stratified 1-year survival, and RAND-36 stratified by normal versus abnormal GWR. Associations were analysed using multivariable analysis**.**
Results: A total of 427 OHCA patients were included in this study, 234 (55%) of whom underwent a brain CT scan within 24 hours after ROSC. Median time between arrest and initial CT scan was 12 hours. In 195 patients (83%), the GWR was described in the reports, but always expressed qualitatively. The GWR was deemed abnormal in 57 (29%) CT scans. No differences were found in secondary endpoints between the two groups**.**
Conclusion: GWR was frequently described in CT scan reports. Early abnormal GWR, as assessed qualitatively by a radiologist within 24 hours after ROSC, was a poor predictor of neurological prognosis.

Gepubliceerd: Resuscitation. 2022;175:13-8.
Impact factor: 6.251 ; Q1

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2. The association of prior paracetamol intake with outcome of very old intensive care patients with COVID-19: results from an international prospective multicentre trial
Baldia PH, Wernly B, Flaatten H, Fjølner J, Artigas A, Pinto BB, Schefold JC, Kelm M, Beil M, Bruno RR, Binnebößel S, Wolff G, Erkens R, Sigal S, van Heerden PV, Szczeklik W, Elhadi M, Joannidis M, Oeyen S, Marsh B, Andersen FH, Moreno R, Leaver S, De Lange DW, Guidet B, Jung C, COVIP study group: Cornet AD.

Background: In the early COVID-19 pandemic concerns about the correct choice of analgesics in patients with COVID-19 were raised. Little data was available on potential usefulness or harmfulness of prescription free analgesics, such as paracetamol. This international multicentre study addresses that lack of evidence regarding the usefulness or potential harm of paracetamol intake prior to ICU admission in a setting of COVID-19 disease within a large, prospectively enrolled cohort of critically ill and frail intensive care unit (ICU) patients**.**
Methods: This prospective international observation study (The COVIP study) recruited ICU patients ≥ 70 years admitted with COVID-19. Data on Sequential Organ Failure Assessment (SOFA) score, prior paracetamol intake within 10 days before admission, ICU therapy, limitations of care and survival during the ICU stay, at 30 days, and 3 months. Paracetamol intake was analysed for associations with ICU-, 30-day- and 3-month-mortality using Kaplan Meier analysis. Furthermore, sensitivity analyses were used to stratify 30-day-mortality in subgroups for patient-specific characteristics using logistic regression**.**

Results: 44% of the 2,646 patients with data recorded regarding paracetamol intake within 10 days prior to ICU admission took paracetamol. There was no difference in age between patients with and without paracetamol intake. Patients taking paracetamol suffered from more co-morbidities, namely diabetes mellitus (43% versus 34%, $p < 0.001$), arterial hypertension (70% versus 65%, $p = 0.006$) and had a higher score on Clinical Frailty Scale (CFS; IQR 2-5 versus IQR 2-4, $p < 0.001$). Patients under prior paracetamol treatment were less often subjected to intubation and vasopressor use, compared to patients without paracetamol intake (65 versus 71%, $p < 0.001$; 63 versus 69%, $p = 0.007$). Paracetamol intake was not associated with ICU-, 30-day- and 3-month-mortality, remaining true after multivariate adjusted analysis**.**
Conclusion: Paracetamol intake prior to ICU admission was not associated with short-term and 3-month mortality in old, critically ill intensive care patients suffering from COVID-19.
Trial registration: This prospective international multicentre study was registered on ClinicalTrials.gov with the identifier "NCT04321265" on March 25, 2020.

Gepubliceerd: BMC Geriatr. 2022;22(1):1000.
Impact factor: 4.070 ; Q2

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3. Comparison of outcome and characteristics between 6343 COVID-19 patients and 2256 other community-acquired viral pneumonia patients admitted to Dutch ICUs
Brinkman S, Termorshuizen F, Dongelmans DA, Bakhshi-Raiez F, Arbous MS, de Lange DW, de Keizer NF, Dutch COVID-19 Research Consortium: Silderhuis VM.

Purpose: Describe the differences in characteristics and outcomes between COVID-19 and other viral pneumonia patients admitted to Dutch ICUs.
Material and Methods: Data from the National-Intensive-Care-Evaluation-registry of COVID-19 patients admitted between February 15th and January 1th 2021 and other viral pneumonia patients admitted between January 1st 2017 and January 1st 2020 were used. Patients' characteristics, the unadjusted, and adjusted in-hospital mortality were compared**.**
Results: 6343 COVID-19 and 2256 other viral pneumonia patients from 79 ICUs were included. The COVID-19 patients included more male (71.3 vs 49.8%), had a higher Body-Mass-Index (28.1 vs 25.5), less comorbidities (42.2 vs 72.7%), and a prolonged hospital length of stay (19 vs 9 days). The COVID-19 patients had a significantly higher crude in-hospital mortality rate (Odds ratio (OR) = 1.80), after adjustment for patient characteristics and ICU occupancy rate the OR was respectively 3.62 and 3.58**.**
Conclusion: Higher mortality among COVID-19 patients could not be explained by patient characteristics and higher ICU occupancy rates, indicating that COVID-19 is more severe compared to other viral pneumonia. Our findings confirm earlier warnings of a high need of ICU capacity and high mortality rates among relatively healthy COVID-19 patients as this may lead to a higher mental workload for the staff.

Gepubliceerd: J Crit Care. 2022;68:76-82.
Impact factor: 4.298 ; Q2

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4. The association of the Activities of Daily Living and the outcome of old intensive care patients suffering from COVID-19
Bruno RR, Wernly B, Flaatten H, Fjølner J, Artigas A, Baldia PH, Binneboessel S, Bollen Pinto B, Schefold JC, Wolff G, Kelm M, Beil M, Sviri S, van Heerden PV, Szczeklik W, Elhadi M, Joannidis M, Oeyen S, Kondili E, Marsh B, Wollborn J, Andersen FH, Moreno R, Leaver S, Boumendil A, De Lange DW, Guidet B, Jung C, COVIP study group: Cornet AD.

Purpose: Critically ill old intensive care unit (ICU) patients suffering from Sars-CoV-2 disease (COVID-19) are at increased risk for adverse outcomes. This post hoc analysis investigates the association of the Activities of Daily Living (ADL) with the outcome in this vulnerable patient group**.**
Methods: The COVIP study is a prospective international observational study that recruited ICU patients ≥ 70 years admitted with COVID-19 (NCT04321265). Several parameters including ADL (ADL; 0 = disability, 6 = no disability), Clinical Frailty Scale (CFS), SOFA score, intensive care treatment, ICU- and 3-month survival were recorded. A mixed-effects Weibull proportional hazard regression analyses for 3-month mortality adjusted for multiple confounders**.**
Results: This pre-specified analysis included 2359 patients with a documented ADL and CFS. Most patients evidenced independence in their daily living before hospital admission (80% with ADL = 6). Patients with no frailty and no disability showed the lowest, patients with frailty (CFS ≥ 5) and disability (ADL < 6) the highest 3-month mortality (52 vs. 78%, p < 0.001). ADL was independently associated with 3-month mortality (ADL as a continuous variable: aHR 0.88 (95% CI 0.82-0.94, p < 0.001). Being "disable" resulted in a significant increased risk for 3-month mortality (aHR 1.53 (95% CI 1.19-1.97, p 0.001) even after adjustment for multiple confounders**.**
Conclusion: Baseline Activities of Daily Living (ADL) on admission provides additional information for outcome prediction, although most critically ill old intensive care patients suffering from COVID-19 had no restriction in their ADL prior to ICU admission. Combining frailty and disability identifies a subgroup with particularly high mortality.
Trial registration number: NCT04321265.

Gepubliceerd: Ann Intensive Care. 2022;12(1):26.
Impact factor: 10.318 ; Q1

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5. Cost Analysis From a Randomized Comparison of Immediate Versus Delayed Angiography After Cardiac Arrest
Camaro C, Bonnes JL, Adang EM, Spoormans EM, Janssens GN, van der Hoeven NW, Jewbali LS, Dubois EA, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak R, Vlachojannis GJ, Eikemans BJ, van der Harst P, van der Horst IC, Voskuil M, van der Heijden JJ, Beishuizen B, Stoel M, van der Hoeven H, Henriques JP, Vlaar AP, Vink MA, van den Bogaard B, Heestermans TA, de Ruijter W, Delnoij TS, Crijns HJ, Jessurun GA, Oemrawsingh PV, Gosselink MT, Plomp K, Magro M, Elbers PW, van de Ven PM, Lemkes JS, van Royen N.

Background: In patients with out-of-hospital cardiac arrest without ST-segment elevation, immediate coronary angiography did not improve clinical outcomes when compared with delayed angiography in the COACT (Coronary Angiography After Cardiac Arrest) trial. Whether 1 of the 2 strategies has benefits in terms of health care resource use and costs is currently unknown. We assess the health care resource use and costs in patients with out-of-hospital cardiac arrest**.**
Methods and Results: A total of 538 patients were randomly assigned to a strategy of either immediate or delayed coronary angiography. Detailed health care resource use and cost-prices were collected from the initial hospital episode. A generalized linear model and a gamma distribution were performed. Generic quality of life was measured with the RAND-36 and collected at 12-month follow-up. Overall total mean costs were similar between both groups (EUR 33 575±19 612 versus EUR 33 880±21 044; P=0.86). Generalized linear model: (β, 0.991; 95% CI, 0.894-1.099; P=0.86). Mean procedural costs (coronary angiography and percutaneous coronary intervention, coronary artery bypass graft) were higher in the immediate angiography group (EUR 4384±3447 versus EUR 3028±4220; P<0.001). Costs concerning intensive care unit and ward stay did not show any significant difference. The RAND-36 questionnaire did not differ between both groups**.**
Conclusions: The mean total costs between patients with out-of-hospital cardiac arrest randomly assigned to an immediate angiography or a delayed invasive strategy were similar during the initial

hospital stay. With respect to the higher invasive procedure costs in the immediate group, a strategy awaiting neurological recovery followed by coronary angiography and planned revascularization may be considered. Registration URL: https://trialregister.nl;
Unique identifier: NL4857.

Gepubliceerd: J Am Heart Assoc. 2022;11(5):e022238.
Impact factor: 6.107 ; Q2

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6. Extubation in neurocritical care patients: the ENIO international prospective study
Cinotti R, Mijangos JC, Pelosi P, Haenggi M, Gurjar M, Schultz MJ, Kaye C, Godoy DA, Alvarez P, Ioakeimidou A, Ueno Y, Badenes R, Suei Elbuzidi AA, Piagnerelli M, Elhadi M, Reza ST, Azab MA, McCredie V, Stevens RD, Digitale JC, Fong N, Asehnoune K, ENIO Study Group, the PROtective VENTilation network, the European Society of Intensive Care Medicine, the Colegio Mexicano de Medicina Critica, the Atlanréa group and the Société Française d'Anesthésie-Réanimation–SFAR research network: Vermeijden WJ, Cornet AD.

Purpose: Neurocritical care patients receive prolonged invasive mechanical ventilation (IMV), but there is poor specific information in this high-risk population about the liberation strategies of invasive mechanical ventilation**.**
Methods: ENIO (NCT03400904) is an international, prospective observational study, in 73 intensive care units (ICUs) in 18 countries from 2018 to 2020. Neurocritical care patients with a Glasgow Coma Score (GCS) ≤ 12, receiving IMV ≥ 24 h, undergoing extubation attempt or tracheostomy were included. The primary endpoint was extubation failure by day 5. An extubation success prediction score was created, with 2/3 of patients randomly allocated to the training cohort and 1/3 to the validation cohort. Secondary endpoints were the duration of IMV and in-ICU mortality**.**
Results: 1512 patients were included. Among the 1193 (78.9%) patients who underwent an extubation attempt, 231 (19.4%) failures were recorded. The score for successful extubation prediction retained 20 variables as independent predictors. The area under the curve (AUC) in the training cohort was 0.79 95% confidence interval (CI(95)) [0.71-0.87] and 0.71 CI(95) [0.61-0.81] in the validation cohort. Patients with extubation failure displayed a longer IMV duration (14 [7-21] vs 6 [3-11] days) and a higher in-ICU mortality rate (8.7% vs 2.4%). Three hundred and nineteen (21.1%) patients underwent tracheostomy without extubation attempt. Patients with direct tracheostomy displayed a longer duration of IMV and higher in-ICU mortality than patients with an extubation attempt (success and failure).
Conclusions: In neurocritical care patients, extubation failure is high and is associated with unfavourable outcomes. A score could predict extubation success in multiple settings. However, it will be mandatory to validate our findings in another prospective independent cohort.

Gepubliceerd: Intensive Care Med. 2022;48(11):1539-50.
Impact factor: 41.787 ; Q1

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7. Co-infection and ICU-acquired infection in COIVD-19 ICU patients: a secondary analysis of the UNITE-COVID data set
Conway Morris A, Kohler K, De Corte T, Ercole A, De Grooth HJ, Elbers PWG, Povoa P, Morais R, Koulenti D, Jog S, Nielsen N, Jubb A, Cecconi M, De Waele J, ESICM UNITE COVID investigators: Beishuizen A, Cornet AD.

Background: The COVID-19 pandemic presented major challenges for critical care facilities worldwide. Infections which develop alongside or subsequent to viral pneumonitis are a challenge

under sporadic and pandemic conditions; however, data have suggested that patterns of these differ between COVID-19 and other viral pneumonitides. This secondary analysis aimed to explore patterns of co-infection and intensive care unit-acquired infections (ICU-AI) and the relationship to use of corticosteroids in a large, international cohort of critically ill COVID-19 patients**.**
Methods: This is a multicenter, international, observational study, including adult patients with PCR-confirmed COVID-19 diagnosis admitted to ICUs at the peak of wave one of COVID-19 (February 15th to May 15th, 2020). Data collected included investigator-assessed co-infection at ICU admission, infection acquired in ICU, infection with multi-drug resistant organisms (MDRO) and antibiotic use. Frequencies were compared by Pearson's Chi-squared and continuous variables by Mann-Whitney U test. Propensity score matching for variables associated with ICU-acquired infection was undertaken using R library MatchIT using the "full" matching method**.**
Results: Data were available from 4994 patients. Bacterial co-infection at admission was detected in 716 patients (14%), whilst 85% of patients received antibiotics at that stage. ICU-AI developed in 2715 (54%). The most common ICU-AI was bacterial pneumonia (44% of infections), whilst 9% of patients developed fungal pneumonia; 25% of infections involved MDRO. Patients developing infections in ICU had greater antimicrobial exposure than those without such infections. Incident density (ICU-AI per 1000 ICU days) was in considerable excess of reports from pre-pandemic surveillance. Corticosteroid use was heterogenous between ICUs. In univariate analysis, 58% of patients receiving corticosteroids and 43% of those not receiving steroids developed ICU-AI. Adjusting for potential confounders in the propensity-matched cohort, 71% of patients receiving corticosteroids developed ICU-AI vs 52% of those not receiving corticosteroids. Duration of corticosteroid therapy was also associated with development of ICU-AI and infection with an MDRO.
Conclusions: In patients with severe COVID-19 in the first wave, co-infection at admission to ICU was relatively rare but antibiotic use was in substantial excess to that indication. ICU-AI were common and were significantly associated with use of corticosteroids. Trial registration ClinicalTrials.gov: NCT04836065 (retrospectively registered April 8th 2021).

Gepubliceerd: Crit Care. 2022;26(1):236.
Impact factor: 19.344; Q1

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8. Predicting responders to prone positioning in mechanically ventilated patients with COVID-19 using machine learning
Dam TA, Roggeveen LF, van Diggelen F, Fleuren LM, Jagesar AR, Otten M, de Vries HJ, Gommers D, Cremer OL, Bosman RJ, Rigter S, Wils EJ, Frenzel T, Dongelmans DA, de Jong R, Peters MAA, Kamps MJA, Ramnarain D, Nowitzky R, Nooteboom F, de Ruijter W, Urlings-Strop LC, Smit EGM, Mehagnoul-Schipper DJ, Dormans T, de Jager CPC, Hendriks SHA, Achterberg S, Oostdijk E, Reidinga AC, Festen-Spanjer B, Brunnekreef GB, Cornet AD, van den Tempel W, Boelens AD, Koetsier P, Lens J, Faber HJ, Karakus A, Entjes R, de Jong P, Rettig TCD, Arbous S, Vonk SJJ, Machado T, Herter WE, de Grooth HJ, Thoral PJ, Girbes ARJ, Hoogendoorn M, Elbers PWG, Dutch ICU Data Sharing Against COVID-19 Collaborators: Beishuizen A.

Background: For mechanically ventilated critically ill COVID-19 patients, prone positioning has quickly become an important treatment strategy, however, prone positioning is labor intensive and comes with potential adverse effects. Therefore, identifying which critically ill intubated COVID-19 patients will benefit may help allocate labor resources**.**
Methods: From the multi-center Dutch Data Warehouse of COVID-19 ICU patients from 25 hospitals, we selected all 3619 episodes of prone positioning in 1142 invasively mechanically ventilated patients. We excluded episodes longer than 24 h. Berlin ARDS criteria were not formally documented. We used supervised machine learning algorithms Logistic Regression, Random Forest, Naive Bayes, K-Nearest Neighbors, Support Vector Machine and Extreme Gradient Boosting on

readily available and clinically relevant features to predict success of prone positioning after 4 h (window of 1 to 7 h) based on various possible outcomes. These outcomes were defined as improvements of at least 10% in PaO(2)/FiO(2) ratio, ventilatory ratio, respiratory system compliance, or mechanical power. Separate models were created for each of these outcomes. Re-supination within 4 h after pronation was labeled as failure. We also developed models using a 20 mmHg improvement cut-off for PaO(2)/FiO(2) ratio and using a combined outcome parameter. For all models, we evaluated feature importance expressed as contribution to predictive performance based on their relative ranking**.**
Results: The median duration of prone episodes was 17 h (11-20, median and IQR, N = 2632). Despite extensive modeling using a plethora of machine learning techniques and a large number of potentially clinically relevant features, discrimination between responders and non-responders remained poor with an area under the receiver operator characteristic curve of 0.62 for PaO(2)/FiO(2) ratio using Logistic Regression, Random Forest and XGBoost. Feature importance was inconsistent between models for different outcomes. Notably, not even being a previous responder to prone positioning, or PEEP-levels before prone positioning, provided any meaningful contribution to predicting a successful next proning episode.
Conclusions: In mechanically ventilated COVID-19 patients, predicting the success of prone positioning using clinically relevant and readily available parameters from electronic health records is currently not feasible. Given the current evidence base, a liberal approach to proning in all patients with severe COVID-19 ARDS is therefore justified and in particular regardless of previous results of proning.

Gepubliceerd: Ann Intensive Care. 2022;12(1):99.
Impact factor: 10.318 ; Q1

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9. Poor timing and failure of source control are risk factors for mortality in critically ill patients with secondary peritonitis
De Pascale G, Antonelli M, Deschepper M, Arvaniti K, Blot K, Brown BC, de Lange D, De Waele J, Dikmen Y, Dimopoulos G, Eckmann C, Francois G, Girardis M, Koulenti D, Labeau S, Lipman J, Lipovetsky F, Maseda E, Montravers P, Mikstacki A, Paiva JA, Pereyra C, Rello J, Timsit JF, Vogelaers D, Blot S, Abdominal Sepsis Study (AbSeS) group and the Trials Group of the European Society of Intensive Care Medicine: Vermeijden W, Cornet AD.

Purpose: To describe data on epidemiology, microbiology, clinical characteristics and outcome of adult patients admitted in the intensive care unit (ICU) with secondary peritonitis, with special emphasis on antimicrobial therapy and source control**.**
Methods: Post hoc analysis of a multicenter observational study (Abdominal Sepsis Study, AbSeS) including 2621 adult ICU patients with intra-abdominal infection in 306 ICUs from 42 countries. Time-till-source control intervention was calculated as from time of diagnosis and classified into 'emergency' (< 2 h), 'urgent' (2-6 h), and 'delayed' (> 6 h). Relationships were assessed by logistic regression analysis and reported as odds ratios (OR) and 95% confidence interval (CI)**.**
Results: The cohort included 1077 cases of microbiologically confirmed secondary peritonitis. Mortality was 29.7%. The rate of appropriate empiric therapy showed no difference between survivors and non-survivors (66.4% vs. 61.3%, p = 0.1). A stepwise increase in mortality was observed with increasing Sequential Organ Failure Assessment (SOFA) scores (19.6% for a value ≤ 4-55.4% for a value > 12, p < 0.001). The highest odds of death were associated with septic shock (OR 3.08 [1.42-7.00]), late-onset hospital-acquired peritonitis (OR 1.71 [1.16-2.52]) and failed source control evidenced by persistent inflammation at day 7 (OR 5.71 [3.99-8.18]). Compared with 'emergency' source control intervention (< 2 h of diagnosis), 'urgent' source control was the only modifiable covariate associated with lower odds of mortality (OR 0.50 [0.34-0.73])**.**

Conclusion: 'Urgent' and successful source control was associated with improved odds of survival. Appropriateness of empirical antimicrobial treatment did not significantly affect survival suggesting that source control is more determinative for outcome.

Gepubliceerd: Intensive Care Med. 2022;48(11):1593-606.
Impact factor: 41.787 ; Q1

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10. Characteristics and outcome of COVID-19 patients admitted to the ICU: a nationwide cohort study on the comparison between the first and the consecutive upsurges of the second wave of the COVID-19 pandemic in the Netherlands
Dongelmans DA, Termorshuizen F, Brinkman S, Bakhshi-Raiez F, Arbous MS, de Lange DW, van Bussel BCT, de Keizer NF, Dutch COVID-19 Research Consortium: Silderhuis VM.

Background: To assess trends in the quality of care for COVID-19 patients at the ICU over the course of time in the Netherlands**.**
Methods: Data from the National Intensive Care Evaluation (NICE)-registry of all COVID-19 patients admitted to an ICU in the Netherlands were used. Patient characteristics and indicators of quality of care during the first two upsurges (N = 4215: October 5, 2020-January 31, 2021) and the final upsurge of the second wave, called the 'third wave' (N = 4602: February 1, 2021-June 30, 2021) were compared with those during the first wave (N = 2733, February-May 24, 2020)**.**
Results: During the second and third wave, there were less patients treated with mechanical ventilation (58.1 and 58.2%) and vasoactive drugs (48.0 and 44.7%) compared to the first wave (79.1% and 67.2%, respectively). The occupancy rates as fraction of occupancy in 2019 (1.68 and 1.55 vs. 1.83), the numbers of ICU relocations (23.8 and 27.6 vs. 32.3%) and the mean length of stay at the ICU (HRs of ICU discharge = 1.26 and 1.42) were lower during the second and third wave. No difference in adjusted hospital mortality between the second wave and the first wave was found, whereas the mortality during the third wave was considerably lower (OR = 0.80, 95% CI [0.71-0.90]).
Conclusions: These data show favorable shifts in the treatment of COVID-19 patients at the ICU over time. The adjusted mortality decreased in the third wave. The high ICU occupancy rate early in the pandemic does probably not explain the high mortality associated with COVID-19.

Gepubliceerd: Ann Intensive Care. 2022;12(1):5.
Impact factor: 10.318 ; Q1

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11. ISARIC-COVID-19 dataset: A Prospective, Standardized, Global Dataset of Patients Hospitalized with COVID-19
Garcia-Gallo E, Merson L, Kennon K, Kelly S, Citarella BW, Fryer DV, Shrapnel S, Lee J, Duque S, Fuentes YV, Balan V, Smith S, Wei J, Gonçalves BP, Russell CD, Sigfrid L, Dagens A, Olliaro PL, Baruch J, Kartsonaki C, Dunning J, Rojek A, Rashan A, Beane A, Murthy S, Reyes LF, ISARIC Clinical Characterization Group: Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H.

The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) COVID-19 dataset is one of the largest international databases of prospectively collected clinical data on people hospitalized with COVID-19. This dataset was compiled during the COVID-19 pandemic by a network of hospitals that collect data using the ISARIC-World Health Organization Clinical Characterization Protocol and data tools. The database includes data from more than 705,000 patients, collected in more than 60 countries and 1,500 centres worldwide. Patient data are available from acute hospital admissions with COVID-19 and outpatient follow-ups. The data include signs and symptoms, pre-

existing comorbidities, vital signs, chronic and acute treatments, complications, dates of hospitalization and discharge, mortality, viral strains, vaccination status, and other data. Here, we present the dataset characteristics, explain its architecture and how to gain access, and provide tools to facilitate its use.

Gepubliceerd: Sci Data. 2022;9(1):454.
Impact factor: 8.501 ; Q1

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12. Clinical and organizational factors associated with mortality during the peak of first COVID-19 wave: the global UNITE-COVID study
Greco M, De Corte T, Ercole A, Antonelli M, Azoulay E, Citerio G, Morris AC, De Pascale G, Duska F, Elbers P, Einav S, Forni L, Galarza L, Girbes ARJ, Grasselli G, Gusarov V, Jubb A, Kesecioglu J, Lavinio A, Delgado MCM, Mellinghoff J, Myatra SN, Ostermann M, Pellegrini M, Povoa P, Schaller SJ, Teboul JL, Wong A, De Waele JJ, Cecconi M, SICM UNITE-COVID investigators: Beishuizen A, Cornet AD.

Purpose: To accommodate the unprecedented number of critically ill patients with pneumonia caused by coronavirus disease 2019 (COVID-19) expansion of the capacity of intensive care unit (ICU) to clinical areas not previously used for critical care was necessary. We describe the global burden of COVID-19 admissions and the clinical and organizational characteristics associated with outcomes in critically ill COVID-19 patients**.**
Methods: Multicenter, international, point prevalence study, including adult patients with SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) and a diagnosis of COVID-19 admitted to ICU between February 15th and May 15th, 2020**.**
Results: 4994 patients from 280 ICUs in 46 countries were included. Included ICUs increased their total capacity from 4931 to 7630 beds, deploying personnel from other areas. Overall, 1986 (39.8%) patients were admitted to surge capacity beds. Invasive ventilation at admission was present in 2325 (46.5%) patients and was required during ICU stay in 85.8% of patients. 60-day mortality was 33.9% (IQR across units: 20%-50%) and ICU mortality 32.7%. Older age, invasive mechanical ventilation, and acute kidney injury (AKI) were associated with increased mortality. These associations were also confirmed specifically in mechanically ventilated patients. Admission to surge capacity beds was not associated with mortality, even after controlling for other factors.
Conclusions: ICUs responded to the increase in COVID-19 patients by increasing bed availability and staff, admitting up to 40% of patients in surge capacity beds. Although mortality in this population was high, admission to a surge capacity bed was not associated with increased mortality. Older age, invasive mechanical ventilation, and AKI were identified as the strongest predictors of mortality.

Gepubliceerd: Intensive Care Med. 2022;48(6):690-705.
Impact factor: 41.787 ; Q1

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13. ICONIC study-conservative versus conventional oxygenation targets in intensive care patients: study protocol for a randomized clinical trial
Grim CCA, van der Wal LI, Helmerhorst HJF, van Westerloo DJ, Pelosi P, Schultz MJ, de Jonge E, ICONIC Investigators and PROVE Network: Cornet AD, Krol T, Rinket M, Vermeijden JW, Beishuizen A.

Background: Oxygen therapy is a widely used intervention in acutely ill patients in the intensive care unit (ICU). It is established that not only hypoxia, but also prolonged hyperoxia is associated with poor patient-centered outcomes. Nevertheless, a fundamental knowledge gap remains regarding optimal oxygenation for critically ill patients. In this randomized clinical trial, we aim to compare

ventilation that uses conservative oxygenation targets with ventilation that uses conventional oxygen targets with respect to mortality in ICU patients**.**
Methods: The "ConservatIve versus CONventional oxygenation targets in Intensive Care patients" trial (ICONIC) is an investigator-initiated, international, multicenter, randomized clinical two-arm trial in ventilated adult ICU patients. The ICONIC trial will run in multiple ICUs in The Netherlands and Italy to enroll 1512 ventilated patients. ICU patients with an expected mechanical ventilation time of more than 24 h are randomized to a ventilation strategy that uses conservative (PaO(2) 55-80 mmHg (7.3-10.7 kPa)) or conventional (PaO(2) 110-150 mmHg (14.7-20 kPa)) oxygenation targets. The primary endpoint is 28-day mortality. Secondary endpoints are ventilator-free days at day 28, ICU mortality, in-hospital mortality, 90-day mortality, ICU- and hospital length of stay, ischemic events, quality of life, and patient opinion of research and consent in the emergency setting.
Discussion: The ICONIC trial is expected to provide evidence on the effects of conservative versus conventional oxygenation targets in the ICU population. This study may guide targeted oxygen therapy in the future.
Trial registration: Trialregister.nl NTR7376 . Registered on 20 July, 2018.

Gepubliceerd: Trials. 2022;23(1):136.
Impact factor: 2.728 ; Q4

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14. Increased 30-day mortality in very old ICU patients with COVID-19 compared to patients with respiratory failure without COVID-19
Guidet B, Jung C, Flaatten H, Fjølner J, Artigas A, Pinto BB, Schefold JC, Beil M, Sigal S, van Heerden PV, Szczeklik W, Joannidis M, Oeyen S, Kondili E, Marsh B, Andersen FH, Moreno R, Cecconi M, Leaver S, De Lange DW, Boumendil A, VIP2 and COVIP study groups: Cornet AD.

Purpose: The number of patients ≥ 80 years admitted into critical care is increasing. Coronavirus disease 2019 (COVID-19) added another challenge for clinical decisions for both admission and limitation of life-sustaining treatments (LLST). We aimed to compare the characteristics and mortality of very old critically ill patients with or without COVID-19 with a focus on LLST**.**
Methods: Patients 80 years or older with acute respiratory failure were recruited from the VIP2 and COVIP studies. Baseline patient characteristics, interventions in intensive care unit (ICU) and outcomes (30-day survival) were recorded. COVID patients were matched to non-COVID patients based on the following factors: age (± 2 years), Sequential Organ Failure Assessment (SOFA) score (± 2 points), clinical frailty scale (± 1 point), gender and region on a 1:2 ratio. Specific ICU procedures and LLST were compared between the cohorts by means of cumulative incidence curves taking into account the competing risk of discharge and death**.**
Results: 693 COVID patients were compared to 1393 non-COVID patients. COVID patients were younger, less frail, less severely ill with lower SOFA score, but were treated more often with invasive mechanical ventilation (MV) and had a lower 30-day survival. 404 COVID patients could be matched to 666 non-COVID patients. For COVID patients, withholding and withdrawing of LST were more frequent than for non-COVID and the 30-day survival was almost half compared to non-COVID patients**.**
Conclusion: Very old COVID patients have a different trajectory than non-COVID patients. Whether this finding is due to a decision policy with more active treatment limitation or to an inherent higher risk of death due to COVID-19 is unclear.

Gepubliceerd: Intensive Care Med. 2022;48(4):435-47.
Impact factor: 41.787 ; Q1

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15. Preoperative anaemia and outcome after elective cardiac surgery: a Dutch national registry analysis

Hazen Y, Noordzij PG, Gerritse BM, Scohy TV, Houterman S, Bramer S, Berendsen RR, Bouwman RA, Eberl S, Haenen JSE, Hofland J, Ter Horst M, Kingma MF, Van Klarenbosch J, Klok T, De Korte MPJ, Van Der Maaten J, Spanjersberg AJ, Wietsma NE, van der Meer NJM, Rettig TCD, Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration: Speekenbrink RGH

Background: Previous studies have shown that preoperative anaemia in patients undergoing cardiac surgery is associated with adverse outcomes. However, most of these studies were retrospective, had a relatively small sample size, and were from a single centre. The aim of this study was to analyse the relationship between the severity of preoperative anaemia and short- and long-term mortality and morbidity in a large multicentre national cohort of patients undergoing cardiac surgery**.**
Methods: A nationwide, prospective, multicentre registry (Netherlands Heart Registration) of patients undergoing elective cardiac surgery between January 2013 and January 2019 was used for this observational study. Anaemia was defined according to the WHO criteria, and the main study endpoint was 120-day mortality. The association was investigated using multivariable logistic regression analysis**.**
Results: In total, 35 484 patients were studied, of whom 6802 (19.2%) were anaemic. Preoperative anaemia was associated with an increased risk of 120-day mortality (adjusted odds ratio [aOR] 1.7; 95% confidence interval [CI]: 1.4-1.9; P<0.001). The risk of 120-day mortality increased with anaemia severity (mild anaemia aOR 1.6; 95% CI: 1.3-1.9; P<0.001; and moderate-to-severe anaemia aOR 1.8; 95% CI: 1.4-2.4; P<0.001). Preoperative anaemia was associated with red blood cell transfusion and postoperative morbidity, the causes of which included renal failure, pneumonia, and myocardial infarction.
Conclusions: Preoperative anaemia was associated with mortality and morbidity after cardiac surgery. The risk of adverse outcomes increased with anaemia severity. Preoperative anaemia is a potential target for treatment to improve postoperative outcomes.

Gepubliceerd: Br J Anaesth. 2022;128(4):636-43.
Impact factor: 11.719 ; Q1

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16. High Titers of Low Affinity Antibodies in COVID-19 Patients Are Associated With Disease Severity

Hendriks J, Schasfoort R, Koerselman M, Dannenberg M, Cornet AD, Beishuizen A, van der Palen J, Krabbe J, Mulder AHL, Karperien M.

Background: Almost 2 years from the beginning of the coronavirus disease 2019 (COVID-19) pandemic, there is still a lot unknown how the humoral response affects disease progression. In this study, we investigated humoral antibody responses against specific SARS-CoV2 proteins, their strength of binding, and their relationship with COVID severity and clinical information. Furthermore, we studied the interactions of the specific receptor-binding domain (RBD) in more depth by characterizing specific antibody response to a peptide library.
Material and Methods: We measured specific antibodies of isotypes IgM, IgG, and IgA, as well as their binding strength against the SARS-CoV2 antigens RBD, NCP, S1, and S1S2 in sera of 76 COVID-19 patients using surface plasmon resonance imaging. In addition, these samples were analyzed using a peptide epitope mapping assay, which consists of a library of peptides originating from the RBD**.**
Results: A positive association was observed between disease severity and IgG antibody titers against all SARS-CoV2 proteins and additionally for IgM and IgA antibodies directed against RBD. Interestingly, in contrast to the titer of antibodies, the binding strength went down with increasing

disease severity. Within the critically ill patient group, a positive association with pulmonary embolism, d-dimer, and antibody titers was observed**.**
Conclusion: In critically ill patients, antibody production is high, but affinity is low, and maturation is impaired. This may play a role in disease exacerbation and could be valuable as a prognostic marker for predicting severity.

Gepubliceerd: Front Immunol. 2022;13:867716.
Impact factor: 8.787 ; Q1

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17. Intermediate-high risk pulmonary embolism: identification and treatment
Jager NM, Eijsvogel MMM, Wagenaar M, Beishuizen A, Trof RJ.

Patients with intermediate-high risk pulmonary embolism have a different mix of clinical symptoms. Optimal treatment of patients with intermediate high-risk pulmonary embolism is necessary to prevent short-term mortality. According to the current guidelines, the use of standard coagulation is the treatment of choice in hemodynamic stable patients with intermediate-high risk pulmonary embolism. Systemic thrombolytic therapy is recommended in patients with intermediate-high risk pulmonary embolism who circulatory deteriorate or who did not respond appropriately to standard anticoagulation. Catheter-guided thrombolysis is reserved for patients with intermediate-high risk pulmonary embolism who have a contraindication for systemic thrombolysis or did not respond to systemic thrombolysis. The timing and choice for the right treatment are significant treatment dilemmas. The development of pulmonary embolism response teams helps in the decision-making in patients with intermediate high-risk pulmonary embolism.

Gepubliceerd: Ned Tijdschr Geneeskd. 2022;166.
Impact factor: 0 ; Q NVT

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18. The influence of timing of coronary angiography on acute kidney injury in out-of-hospital cardiac arrest patients: a retrospective cohort study
Janssens GN, Daemen J, Lemkes JS, Spoormans EM, Janssen D, den Uil CA, Jewbali LSD, Heestermans T, Umans V, Halfwerk FR, Beishuizen A, Nas J, Bonnes J, van de Ven PM, van Rossum AC, Elbers PWG, van Royen N.

Background: Acute kidney injury (AKI) is a frequent complication in cardiac arrest survivors and associated with adverse outcome. It remains unclear whether the incidence of AKI increases after the post-cardiac arrest contrast administration for coronary angiography and whether this depends on timing of angiography. Aim of this study was to investigate whether early angiography is associated with increased development of AKI compared to deferred angiography in out-of-hospital cardiac arrest (OHCA) survivors**.**
Methods: In this retrospective multicenter cohort study, we investigated whether early angiography (within 2 h) after OHCA was non-inferior to deferred angiography regarding the development of AKI. We used an absolute difference of 5% as the non-inferiority margin. Primary non-inferiority analysis was done by calculating the risk difference with its 90% confidence interval (CI) using a generalized linear model for a binary outcome. As a sensitivity analysis, we repeated the primary analysis using propensity score matching. A multivariable model was built to identify predictors of acute kidney injury**.**
Results: A total of 2375 patients were included from 2009 until 2018, of which 1148 patients were treated with early coronary angiography and 1227 patients with delayed or no angiography. In the early angiography group 18.5% of patients developed AKI after OHCA and 24.1% in the deferred

angiography group. Risk difference was - 3.7% with 90% CI ranging from - 6.7 to - 0.7%, indicating non-inferiority of early angiography. The sensitivity analysis using propensity score matching showed accordant results, but no longer non-inferiority of early angiography. The factors time to return of spontaneous circulation (odds ratio [OR] 1.12, 95% CI 1.06-1.19, p < 0.001), the (not) use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (OR 0.20, 95% CI 0.04-0.91, p = 0.04) and baseline creatinine (OR 1.05, 95% CI 1.03-1.07, p < 0.001) were found to be independently associated with the development of AKI.
Conclusions: Although AKI occurred in approximately 20% of OHCA patients, we found that early angiography was not associated with a higher AKI incidence than a deferred angiography strategy. The present results implicate that it is safe to perform early coronary angiography with respect to the risk of developing AKI after OHCA.

Gepubliceerd: Ann Intensive Care. 2022;12(1):12.
Impact factor: 10.318 ; Q1

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19. Suboptimal plasma concentrations with posaconazole suspension as prophylaxis in critically ill COVID-19 patients at risk of Covid-associated pulmonary aspergillosis
Mian P, Trof RJ, Beishuizen A, Masselink JB, Cornet AD, Sportel ET.

What is known and objective: The safety and efficacy of different antifungal agents in the prophylaxis of invasive fungal infection in patients with haematological disorders are known. We comment on the poor bioavailability of posaconazole suspension to suggest that it is not useful in critically ill COVID patients.
Comment: The increased mortality and high incidence of COVID-associated pulmonary aspergillosis (CAPA) might justify administration of off-label posaconazole for preventing CAPA, being the only drug officially registered for prophylaxis of fungal infections. We decided to initiate off-label posaconazole prophylaxis in COVID-19 patients, who were mechanically ventilated and exposed to high-dose steroids for progressive pulmonary disease or ARDS. We found that posaconazole suspension was inadequate. Very low trough levels were observed after administration, and the dose adjustments necessary for the therapeutic drug monitoring (TDM) of the drug in our critically ill ICU patients were not useful.
What is new and conclusion: Posaconazole suspension should not be used to prevent CAPA in COVID-19 patients on high-dose steroid therapy.

Gepubliceerd: J Clin Pharm Ther. 2022;47(3):383-5.
Impact factor: 2.145 ; Q4

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20. Lupus anticoagulant associates with thrombosis in patients with COVID-19 admitted to intensive care units: A retrospective cohort study
Noordermeer T, Schutgens REG, Visser C, Rademaker E, de Maat MPM, Jansen AJG, Limper M, Cremer OL, Kruip M, Endeman H, Maas C, de Laat B, Urbanus RT, Dutch COVID & Thrombosis Coalition (DCTC): Beishuizen A, Cornet AD, Krabbe J.

Background: Thrombosis is a frequent and severe complication in patients with coronavirus disease 2019 (COVID-19) admitted to the intensive care unit (ICU). Lupus anticoagulant (LA) is a strong acquired risk factor for thrombosis in various diseases and is frequently observed in patients with COVID-19. Whether LA is associated with thrombosis in patients with severe COVID-19 is currently unclear.
Objective: To investigate if LA is associated with thrombosis in critically ill patients with COVID-19.

Patients/methods: The presence of LA and other antiphospholipid antibodies was assessed in patients with COVID-19 admitted to the ICU. LA was determined with dilute Russell's viper venom time (dRVVT) and LA-sensitive activated partial thromboplastin time (aPTT) reagents**.**
Results: Of 169 patients with COVID-19, 116 (69%) tested positive for at least one antiphospholipid antibody upon admission to the ICU. Forty (24%) patients tested positive for LA; of whom 29 (17%) tested positive with a dRVVT, 19 (11%) tested positive with an LA-sensitive aPTT, and 8 (5%) tested positive on both tests. Fifty-eight (34%) patients developed thrombosis after ICU admission. The odds ratio (OR) for thrombosis in patients with LA based on a dRVVT was 2.5 (95% confidence interval [CI], 1.1-5.7), which increased to 4.5 (95% CI, 1.4-14.3) in patients at or below the median age in this study (64 years). LA positivity based on a dRVVT or LA-sensitive aPTT was only associated with thrombosis in patients aged less than 65 years (OR, 3.8; 95% CI, 1.3-11.4) and disappeared after adjustment for C-reactive protein**.**
Conclusion: Lupus anticoagulant on admission is strongly associated with thrombosis in critically ill patients with COVID-19, especially in patients aged less than 65 years.

Gepubliceerd: Res Pract Thromb Haemost. 2022;6(6):e12809.
Impact factor: 5.953 ; Q1

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21. Effects of targeted temperature management at 33 °C vs. 36 °C on comatose patients after cardiac arrest stratified by the severity of encephalopathy
Nutma S, Tjepkema-Cloostermans MC, Ruijter BJ, Tromp SC, van den Bergh WM, Foudraine NA, Kornips FHM, Drost G, Scholten E, Strang A, Beishuizen A, van Putten M, Hofmeijer J.

Objectives: To assess neurological outcome after targeted temperature management (TTM) at 33 °C vs. 36 °C, stratified by the severity of encephalopathy based on EEG-patterns at 12 and 24 h.
Design: Post hoc analysis of prospective cohort study. SETTING: Five Dutch Intensive Care units**.**
Patients: 479 adult comatose post-cardiac arrest patients**.**
Interventions: TTM at 33 °C (n = 270) or 36 °C (n = 209) and continuous EEG monitoring.
Measurements and Main Results: Outcome according to the cerebral performance category (CPC) score at 6 months post-cardiac arrest was similar after 33 °C and 36 °C. However, when stratified by the severity of encephalopathy based on EEG-patterns at 12 and 24 h after cardiac arrest, the proportion of good outcome (CPC 1-2) in patients with moderate encephalopathy was significantly larger after TTM at 33 °C (66% vs. 45%; Odds Ratios 2.38, 95% CI = 1.32-4.30; p = 0.004). In contrast, with mild encephalopathy, there was no statistically significant difference in the proportion of patients with good outcome between 33 °C and 36 °C (88% vs. 81%; OR 1.68, 95% CI = 0.65-4.38; p = 0.282). Ordinal regression analysis showed a shift towards higher CPC scores when treated with TTM 33 °C as compared with 36 °C in moderate encephalopathy (cOR 2.39; 95% CI = 1.40-4.08; p = 0.001), but not in mild encephalopathy (cOR 0.81 95% CI = 0.41-1.59; p = 0.537). Adjustment for initial cardiac rhythm and cause of arrest did not change this relationship.
Conclusions: Effects of TTM probably depend on the severity of encephalopathy in comatose patients after cardiac arrest. These results support inclusion of predefined subgroup analyses based on EEG measures of the severity of encephalopathy in future clinical trials.

Gepubliceerd: Resuscitation. 2022;173:147-53.
Impact factor: 6.251 ; Q1

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22. Comparison of patient characteristics and long-term mortality between transferred and non-transferred COVID-19 patients in Dutch intensive care units: A national cohort study

Wortel SA, Bakhshi-Raiez F, Termorshuizen F, de Lange DW, Dongelmans DA, de Keizer NF, Dutch COVID-19 Research Consortium: Silderhuis VM.

Background: COVID-19 patients were often transferred to other intensive care units (ICUs) to prevent that ICUs would reach their maximum capacity. However, transferring ICU patients is not free of risk. We aim to compare the characteristics and outcomes of transferred versus non-transferred COVID-19 ICU patients in the Netherlands**.**
Methods: We included adult COVID-19 patients admitted to Dutch ICUs between March 1, 2020 and July 1, 2021. We compared the patient characteristics and outcomes of non-transferred and transferred patients and used a Directed Acyclic Graph to identify potential confounders in the relationship between transfer and mortality. We used these confounders in a Cox regression model with left truncation at the day of transfer to analyze the effect of transfers on mortality during the 180 days after ICU admission**.**
Results: We included 10,209 patients: 7395 non-transferred and 2814 (27.6%) transferred patients. In both groups, the median age was 64 years. Transferred patients were mostly ventilated at ICU admission (83.7% vs. 56.2%) and included a larger proportion of low-risk patients (70.3% vs. 66.5% with mortality risk <30%). After adjusting for age, APACHE IV mortality probability, BMI, mechanical ventilation, and vasoactive medication use, the hazard of mortality during the first 180 days was similar for transferred patients compared to non-transferred patients (HR [95% CI] = 0.99 [0.91-1.08]).
Conclusions: Transferred COVID-19 patients are more often mechanically ventilated and are less severely ill compared to non-transferred patients. Furthermore, transferring critically ill COVID-19 patients in the Netherlands is not associated with mortality during the first 180 days after ICU admission.

Gepubliceerd: Acta Anaesthesiol Scand. 2022;66(9):1107-15.
Impact factor: 2.274 ; Q4

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23. Outcome Prediction of Postanoxic Coma: A Comparison of Automated Electroencephalography Analysis Methods
Pham SDT, Keijzer HM, Ruijter BJ, Seeber AA, Scholten E, Drost G, van den Bergh WM, Kornips FHM, Foudraine NA, Beishuizen A, Blans MJ, Hofmeijer J, van Putten M, Tjepkema-Cloostermans MC.

Background: To compare three computer-assisted quantitative electroencephalography (EEG) prediction models for the outcome prediction of comatose patients after cardiac arrest regarding predictive performance and robustness to artifacts**.**
Methods: A total of 871 continuous EEGs recorded up to 3 days after cardiac arrest in intensive care units of five teaching hospitals in the Netherlands were retrospectively analyzed. Outcome at 6 months was dichotomized as "good" (Cerebral Performance Category 1-2) or "poor" (Cerebral Performance Category 3-5). Three prediction models were implemented: a logistic regression model using two quantitative features, a random forest model with nine features, and a deep learning model based on a convolutional neural network. Data from two centers were used for training and fivefold cross-validation (n = 663), and data from three other centers were used for external validation (n = 208). Model output was the probability of good outcome. Predictive performances were evaluated by using receiver operating characteristic analysis and the calculation of predictive values. Robustness to artifacts was evaluated by using an artifact rejection algorithm, manually added noise, and randomly flattened channels in the EEG**.**
Results: The deep learning network showed the best overall predictive performance. On the external test set, poor outcome could be predicted by the deep learning network at 24 h with a sensitivity of 54% (95% confidence interval [CI] 44-64%) at a false positive rate (FPR) of 0% (95% CI 0-2%),

significantly higher than the logistic regression (sensitivity 33%, FPR 0%) and random forest models (sensitivity 13%, FPR, 0%) ($p < 0.05$). Good outcome at 12 h could be predicted by the deep learning network with a sensitivity of 78% (95% CI 52-100%) at a FPR of 12% (95% CI 0-24%) and by the logistic regression model with a sensitivity of 83% (95% CI 83-83%) at a FPR of 3% (95% CI 3-3%), both significantly higher than the random forest model (sensitivity 1%, FPR 0%) ($p < 0.05$). The results of the deep learning network were the least affected by the presence of artifacts, added white noise, and flat EEG channels.
Conclusions: A deep learning model outperformed logistic regression and random forest models for reliable, robust, EEG-based outcome prediction of comatose patients after cardiac arrest.

Gepubliceerd: Neurocrit Care. 2022;37(Suppl 2):248-58.
Impact factor: 3.532 ; Q2

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24. Rapid Evaluation of Coronavirus Illness Severity (RECOILS) in intensive care: Development and validation of a prognostic tool for in-hospital mortality
Plečko D, Bennett N, Mårtensson J, Dam TA, Entjes R, Rettig TCD, Dongelmans DA, Boelens AD, Rigter S, Hendriks SHA, de Jong R, Kamps MJA, Peters M, Karakus A, Gommers D, Ramnarain D, Wils EJ, Achterberg S, Nowitzky R, van den Tempel W, de Jager CPC, Nooteboom F, Oostdijk E, Koetsier P, Cornet AD, Reidinga AC, de Ruijter W, Bosman RJ, Frenzel T, Urlings-Strop LC, de Jong P, Smit EGM, Cremer OL, Mehagnoul-Schipper DJ, Faber HJ, Lens J, Brunnekreef GB, Festen-Spanjer B, Dormans T, de Bruin DP, Lalisang RCA, Vonk SJJ, Haan ME, Fleuren LM, Thoral PJ, Elbers PWG, Bellomo R.

Background: The prediction of in-hospital mortality for ICU patients with COVID-19 is fundamental to treatment and resource allocation. The main purpose was to develop an easily implemented score for such prediction**.**
Methods: This was an observational, multicenter, development, and validation study on a national critical care dataset of COVID-19 patients. A systematic literature review was performed to determine variables possibly important for COVID-19 mortality prediction. Using a logistic multivariable model with a LASSO penalty, we developed the Rapid Evaluation of Coronavirus Illness Severity (RECOILS) score and compared its performance against published scores**.**
Results: Our development (validation) cohort consisted of 1480 (937) adult patients from 14 (11) Dutch ICUs admitted between March 2020 and April 2021. Median age was 65 (65) years, 31% (26%) died in hospital, 74% (72%) were males, average length of ICU stay was 7.83 (10.25) days and average length of hospital stay was 15.90 (19.92) days. Age, platelets, PaO2/FiO2 ratio, pH, blood urea nitrogen, temperature, PaCO2, Glasgow Coma Scale (GCS) score measured within +/-24 h of ICU admission were used to develop the score. The AUROC of RECOILS score was 0.75 (CI 0.71-0.78) which was higher than that of any previously reported predictive scores (0.68 [CI 0.64-0.71], 0.61 [CI 0.58-0.66], 0.67 [CI 0.63-0.70], 0.70 [CI 0.67-0.74] for ISARIC 4C Mortality Score, SOFA, SAPS-III, and age, respectively).
Conclusions: Using a large dataset from multiple Dutch ICUs, we developed a predictive score for mortality of COVID-19 patients admitted to ICU, which outperformed other predictive scores reported so far.

Gepubliceerd: Acta Anaesthesiol Scand. 2022;66(1):65-75.
Impact factor: 2.274 ; Q4

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25. Respiratory support in patients with severe COVID-19 in the International Severe Acute Respiratory and Emerging Infection (ISARIC) COVID-19 study: a prospective, multinational, observational study

Reyes LF, Murthy S, Garcia-Gallo E, Merson L, Ibáñez-Prada ED, Rello J, Fuentes YV, Martin-Loeches I, Bozza F, Duque S, Taccone FS, Fowler RA, Kartsonaki C, Gonçalves BP, Citarella BW, Aryal D, Burhan E, Cummings MJ, Delmas C, Diaz R, Figueiredo-Mello C, Hashmi M, Panda PK, Jiménez MP, Rincon DFB, Thomson D, Nichol A, Marshall JC, Olliaro PL, ISARIC Characterization Group: Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H.

Background: Up to 30% of hospitalised patients with COVID-19 require advanced respiratory support, including high-flow nasal cannulas (HFNC), non-invasive mechanical ventilation (NIV), or invasive mechanical ventilation (IMV). We aimed to describe the clinical characteristics, outcomes and risk factors for failing non-invasive respiratory support in patients treated with severe COVID-19 during the first two years of the pandemic in high-income countries (HICs) and low middle-income countries (LMICs)**.**
Methods: This is a multinational, multicentre, prospective cohort study embedded in the ISARIC-WHO COVID-19 Clinical Characterisation Protocol. Patients with laboratory-confirmed SARS-CoV-2 infection who required hospital admission were recruited prospectively. Patients treated with HFNC, NIV, or IMV within the first 24 h of hospital admission were included in this study. Descriptive statistics, random forest, and logistic regression analyses were used to describe clinical characteristics and compare clinical outcomes among patients treated with the different types of advanced respiratory support**.**
Results: A total of 66,565 patients were included in this study. Overall, 82.6% of patients were treated in HIC, and 40.6% were admitted to the hospital during the first pandemic wave. During the first 24 h after hospital admission, patients in HICs were more frequently treated with HFNC (48.0%), followed by NIV (38.6%) and IMV (13.4%). In contrast, patients admitted in lower- and middle-income countries (LMICs) were less frequently treated with HFNC (16.1%) and the majority received IMV (59.1%). The failure rate of non-invasive respiratory support (i.e. HFNC or NIV) was 15.5%, of which 71.2% were from HIC and 28.8% from LMIC. The variables most strongly associated with non-invasive ventilation failure, defined as progression to IMV, were high leukocyte counts at hospital admission (OR [95%CI]; 5.86 [4.83-7.10]), treatment in an LMIC (OR [95%CI]; 2.04 [1.97-2.11]), and tachypnoea at hospital admission (OR [95%CI]; 1.16 [1.14-1.18]). Patients who failed HFNC/NIV had a higher 28-day fatality ratio (OR [95%CI]; 1.27 [1.25-1.30]).
Conclusions: In the present international cohort, the most frequently used advanced respiratory support was the HFNC. However, IMV was used more often in LMIC. Higher leucocyte count, tachypnoea, and treatment in LMIC were risk factors for HFNC/NIV failure. HFNC/NIV failure was related to worse clinical outcomes, such as 28-day mortality. Trial registration This is a prospective observational study; therefore, no health care interventions were applied to participants, and trial registration is not applicable.

Gepubliceerd: Crit Care. 2022;26(1):276.
Impact factor: 19.344; Q1

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26. In-depth assessment of health-related quality of life after in-hospital cardiac arrest
Schluep M, Endeman H, Gravesteijn BY, Kuijs C, Blans MJ, van den Bogaard B, Van Gemert A, Hukshorn CJ, van der Meer BJM, Knook AHM, van Melsen T, Peters R, Simons KS, Spijkers G, Vermeijden JW, Wils EJ, Stolker RJ, Hoeks SE.

Introduction: Evidence on physical and psychological well-being of in-hospital cardiac arrest (IHCA) survivors is scarce. The aim of this study is to describe long-term health-related quality of life (HRQoL), functional independence and psychological distress 3 and 12 months post-IHCA**.**

Methods: A multicenter prospective cohort study in 25 hospitals between January 2017 - May 2018. Adult IHCA survivors were included. HRQoL (EQ-5D-5L, SF-12), psychological distress (HADS, CSI) and functional independence (mRS) were assessed at 3 and 12 months post-IHCA**.**
Results: At 3-month follow-up 136 of 212 survivors responded to the questionnaire and at 12 months 110 of 198 responded. The median (IQR) EQ-utility Index score was 0.77 (0.65-0.87) at 3 months and 0.81 (0.70-0.91) at 12 months. At 3 months, patients reported a median SF-12 (IQR) physical component scale (PCS) of 38.9 (32.8-46.5) and mental component scale (MCS) of 43.5 (34.0-39.7) and at 12 months a PCS of 43.1 (34.6-52.3) and MCS 46.9 (38.5-54.5).
Discussion: Using various tools most IHCA survivors report an acceptable HRQoL and a substantial part experiences lower HRQoL compared to population norms. Our data suggest that younger (male) patients and those with poor functional status prior to admission are at highest risk of impaired HRQoL.

Gepubliceerd: J Crit Care. 2022;68:22-30.
Impact factor: 4.298 ; Q2

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27. Incidence, risk factors, and outcome of suspected central venous catheter-related infections in critically ill COVID-19 patients: a multicenter retrospective cohort study
Smit JM, Exterkate L, van Tienhoven AJ, Haaksma ME, Heldeweg MLA, Fleuren L, Thoral P, Dam TA, Heunks LMA, Gommers D, Cremer OL, Bosman RJ, Rigter S, Wils EJ, Frenzel T, Vlaar AP, Dongelmans DA, de Jong R, Peters M, Kamps MJA, Ramnarain D, Nowitzky R, Nooteboom F, de Ruijter W, Urlings-Strop LC, Smit EGM, Mehagnoul-Schipper DJ, Dormans T, de Jager CPC, Hendriks SHA, Achterberg S, Oostdijk E, Reidinga AC, Festen-Spanjer B, Brunnekreef GB, Cornet AD, van den Tempel W, Boelens AD, Koetsier P, Lens J, Faber HJ, Karakus A, Entjes R, de Jong P, Rettig TCD, Arbous S, Vonk B, Machado T, Girbes ARJ, Sieswerda E, Elbers PWG, Tuinman PR.

Background: Aims of this study were to investigate the prevalence and incidence of catheter-related infection, identify risk factors, and determine the relation of catheter-related infection with mortality in critically ill COVID-19 patients**.**
Methods: This was a retrospective cohort study of central venous catheters (CVCs) in critically ill COVID-19 patients. Eligible CVC insertions required an indwelling time of at least 48 hours and were identified using a full-admission electronic health record database. Risk factors were identified using logistic regression. Differences in survival rates at day 28 of follow-up were assessed using a log-rank test and proportional hazard model**.**
Results: In 538 patients, a total of 914 CVCs were included. Prevalence and incidence of suspected catheter-related infection were 7.9% and 9.4 infections per 1,000 catheter indwelling days, respectively. Prone ventilation for more than 5 days was associated with increased risk of suspected catheter-related infection; odds ratio, 5.05 (95% confidence interval 2.12-11.0). Risk of death was significantly higher in patients with suspected catheter-related infection (hazard ratio, 1.78; 95% confidence interval, 1.25-2.53)**.**
Conclusions: This study shows that in critically ill patients with COVID-19, prevalence and incidence of suspected catheter-related infection are high, prone ventilation is a risk factor, and mortality is higher in case of catheter-related infection.

Gepubliceerd: Shock. 2022;58(5):358-65.
Impact factor: 3.533 ; Q1

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28. Dynamic prediction of mortality in COVID-19 patients in the intensive care unit: A retrospective multi-center cohort study

Smit JM, Krijthe JH, Endeman H, Tintu AN, de Rijke YB, Gommers D, Cremer OL, Bosman RJ, Rigter S, Wils EJ, Frenzel T, Dongelmans DA, De Jong R, Peters MAA, Kamps MJA, Ramnarain D, Nowitzky R, Nooteboom F, De Ruijter W, Urlings-Strop LC, Smit EGM, Mehagnoul-Schipper DJ, Dormans T, De Jager CPC, Hendriks SHA, Achterberg S, Oostdijk E, Reidinga AC, Festen-Spanjer B, Brunnekreef GB, Cornet AD, Van den Tempel W, Boelens AD, Koetsier P, Lens JA, Faber HJ, Karakus A, Entjes R, De Jong P, Rettig TCD, Arbous MS, Lalisang RCA, Tonutti M, De Bruin DP, Elbers PWG, Van Bommel J, Reinders MJT.

Background: The COVID-19 pandemic continues to overwhelm intensive care units (ICUs) worldwide, and improved prediction of mortality among COVID-19 patients could assist decision making in the ICU setting. In this work, we report on the development and validation of a dynamic mortality model specifically for critically ill COVID-19 patients and discuss its potential utility in the ICU**.**
Methods: We collected electronic medical record (EMR) data from 3222 ICU admissions with a COVID-19 infection from 25 different ICUs in the Netherlands. We extracted daily observations of each patient and fitted both a linear (logistic regression) and non-linear (random forest) model to predict mortality within 24 h from the moment of prediction. Isotonic regression was used to re-calibrate the predictions of the fitted models. We evaluated the models in a leave-one-ICU-out (LOIO) cross-validation procedure**.**
Results: The logistic regression and random forest model yielded an area under the receiver operating characteristic curve of 0.87 [0.85; 0.88] and 0.86 [0.84; 0.88], respectively. The recalibrated model predictions showed a calibration intercept of -0.04 [-0.12; 0.04] and slope of 0.90 [0.85; 0.95] for logistic regression model and a calibration intercept of -0.19 [-0.27; -0.10] and slope of 0.89 [0.84; 0.94] for the random forest model.
Discussion: We presented a model for dynamic mortality prediction, specifically for critically ill COVID-19 patients, which predicts near-term mortality rather than in-ICU mortality. The potential clinical utility of dynamic mortality models such as benchmarking, improving resource allocation and informing family members, as well as the development of models with more causal structure, should be topics for future research.

Gepubliceerd: Intell Based Med. 2022;6:100071.
Impact factor: 0 ; Q NVT

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29. Health-related quality of life in older patients surviving ICU treatment for COVID-19: results from an international observational study of patients older than 70 years

Soliman IW, Leaver S, Flaatten H, Fjølner J, Wernly B, Bruno RR, Artigas A, Bollen Pinto B, Schefold JC, Beil M, Sviri S, van Heerden PV, Szczeklik W, Elhadi M, Joannidis M, Oeyen S, Zafeiridis T, Wollborn J, Banzo MJA, Fuest K, Marsh B, Andersen FH, Moreno R, Boumendil A, Guidet B, Jung C, De Lange DW, COVIP-study group: Cornet AD.

Background: health-related quality of life (HRQoL) is an important patient-centred outcome in patients surviving ICU admission for COVID-19. It is currently not clear which domains of the HRQoL are most affected.
Objective: to quantify HRQoL in order to identify areas of interventions.
Design:prospective observation study. SETTING: admissions to European ICUs between March 2020 and February 2021. SUBJECTS: patients aged 70 years or older admitted with COVID-19 disease**.**
Methods: collected determinants include SOFA-score, Clinical Frailty Scale (CFS), number and timing of ICU procedures and limitation of care, Katz Activities of Daily Living (ADL) dependence score. HRQoL was assessed at 3 months after ICU admission with the Euro-QoL-5D-5L questionnaire. An outcome of ≥4 on any of Euro-QoL-5D-5L domains was considered unfavourable**.**

Results: in total 3,140 patients from 14 European countries were included in this study. Three months after inclusion, 1,224 patients (39.0%) were alive and the EQ-5D-5L from was obtained. The CFS was associated with an increased odds ratio for an unfavourable HRQoL outcome after 3 months; OR 1.15 (95% confidence interval (CI): 0.71-1.87) for CFS 2 to OR 4.33 (95% CI: 1.57-11.9) for CFS ≧ 7. The Katz ADL was not statistically significantly associated with HRQoL after 3 months.
Conclusions: in critically ill old intensive care patients suffering from COVID-19, the CFS is associated with the subjectively perceived quality of life. The CFS on admission can be used to inform patients and relatives on the risk of an unfavourable qualitative outcome if such patients survive.

Gepubliceerd: Age Ageing. 2022;51(2).
Impact factor: 12.782 ; Q1

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30. Ischaemic electrocardiogram patterns and its association with survival in out-of-hospital cardiac arrest patients without ST-segment elevation myocardial infarction: a COACT trials' post-hoc subgroup analysis
Spoormans EM, Lemkes JS, Janssens GN, Soultana O, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak R, Vlachojannis GJ, Eikemans BJW, van der Harst P, van der Horst ICC, Voskuil M, van der Heijden JJ, Beishuizen A, Stoel M, Camaro C, van der Hoeven H, Henriques JP, Vlaar APJ, Vink MA, van den Bogaard B, Heestermans T, de Ruijter W, Delnoij TSR, Crijns H, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, van de Ven PM, van Royen N.

Aims: ST-depression and T-wave inversion are frequently present on the post-resuscitation electrocardiogram (ECG). However, the prognostic value of ischaemic ECG patterns is unknown**.**
Methods and Results: In this post-hoc subgroup analysis of the Coronary Angiography after Cardiac arrest (COACT) trial, the first in-hospital post-resuscitation ECG in out-of-hospital cardiac arrest patients with a shockable rhythm was analysed for ischaemic ECG patterns. Ischaemia was defined as ST-depression of ≥0.1 mV, T-wave inversion in ≥2 contiguous leads, or both. The primary endpoint was 90-day survival. Secondary endpoints were rate of acute unstable lesions, levels of serum troponin-T, and left ventricular function. Of the 510 out-of-hospital cardiac arrest patients, 340 (66.7%) patients had ischaemic ECG patterns. Patients with ischaemic ECG patterns had a worse 90-day survival compared with those without [hazard ratio 1.51; 95% confidence interval (CI) 1.08-2.12; P = 0.02]. A higher sum of ST-depression was associated with lower survival (log-rank = 0.01). The rate of acute unstable lesions (14.5 vs. 15.8%; odds ratio 0.90; 95% CI 0.51-1.59) did not differ between the groups. In patients with ischaemic ECG patterns, maximum levels of serum troponin-T (μg/L) were higher [0.595 (interquartile range 0.243-1.430) vs. 0.359 (0.159-0.845); ratio of geometric means 1.58; 1.13-2.20] and left ventricular function (%) was worse (44.7 ± 12.5 vs. 49.9 ± 13.3; mean difference -5.13; 95% CI -8.84 to -1.42). Adjusted for age and time to return of spontaneous circulation, ischaemic ECG patterns were no longer associated with survival**.**
Conclusion: Post-arrest ischaemic ECG patterns were associated with worse 90-day survival. A higher sum of ST-depression was associated with lower survival. Adjusted for age and time to return of spontaneous circulation, ischaemic ECG patterns were no longer associated with survival.

Gepubliceerd: Eur Heart J Acute Cardiovasc Care. 2022;11(7):535-43.
Impact factor: 4.766 ; Q2

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31. Targeted Temperature Management in Out-of-Hospital Cardiac Arrest With Shockable Rhythm: A Post Hoc Analysis of the Coronary Angiography After Cardiac Arrest Trial

Spoormans EM, Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak R, Vlachojannis GJ, Eikemans BJW, Girbes ARJ, van der Harst P, van der Horst ICC, Voskuil M, van der Heijden JJ, Beishuizen A, Stoel M, Camaro C, van der Hoeven H, Henriques JP, Vlaar APJ, Vink MA, van den Bogaard B, Heestermans T, de Ruijter W, Delnoij TSR, Crijns H, Jessurun GAJ, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, van de Ven PM, van Royen N, Elbers PWG.

Objectives: The optimal targeted temperature in patients with shockable rhythm is unclear, and current guidelines recommend targeted temperature management with a correspondingly wide range between 32°C and 36°C. Our aim was to study survival and neurologic outcome associated with targeted temperature management strategy in postarrest patients with initial shockable rhythm.
Design: Observational substudy of the Coronary Angiography after Cardiac Arrest without ST-segment Elevation trial. SETTING: Nineteen hospitals in The Netherlands**.**
Patients: The Coronary Angiography after Cardiac Arrest trial randomized successfully resuscitated patients with shockable rhythm and absence of ST-segment elevation to a strategy of immediate or delayed coronary angiography. In this substudy, 459 patients treated with mild therapeutic hypothermia (32.0-34.0°C) or targeted normothermia (36.0-37.0°C) were included. Allocation to targeted temperature management strategy was at the discretion of the physician**.**
Interventions: None**.**
measurements and Main Results: After 90 days, 171 patients (63.6%) in the mild therapeutic hypothermia group and 129 (67.9%) in the targeted normothermia group were alive (hazard ratio, 0.86 [95% CI, 0.62-1.18]; log-rank p = 0.35; adjusted odds ratio, 0.89; 95% CI, 0.45-1.72). Patients in the mild therapeutic hypothermia group had longer ICU stay (4 d [3-7 d] vs 3 d [2-5 d]; ratio of geometric means, 1.32; 95% CI, 1.15-1.51), lower blood pressures, higher lactate levels, and increased need for inotropic support. Cerebral Performance Category scores at ICU discharge and 90-day follow-up and patient-reported Mental and Physical Health Scores at 1 year were similar in the two groups.
Conclusions: In the context of out-of-hospital cardiac arrest with shockable rhythm and no ST-elevation, treatment with mild therapeutic hypothermia was not associated with improved 90-day survival compared with targeted normothermia. Neurologic outcomes at 90 days as well as patient-reported Mental and Physical Health Scores at 1 year did not differ between the groups.

Gepubliceerd: Crit Care Med. 2022;50(2):e129-e42.
Impact factor: 9.296; Q1

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32. Delayed Diagnosis of Severe Hypoglycemia in a Septic Patient With Chronic Renal Failure
Ten Berge D, Manning F, Silderhuis V, Deijns S, Pouwels MJ, Krabbe H, Beishuizen A.

High-dose vitamin C therapy has gained increased interest as an adjunctive treatment of septic shock, although convincing evidence is still lacking. High blood levels of vitamin C may interfere with several point-of-care blood glucose meters. We describe the case of a 67-year-old septic patient known with chronic renal failure who developed truly severe hypoglycemia, which was masked by spuriously high glucose values measured on a capillary blood glucose meter. This initially led to the treatment of spurious hyperglycemia with high-dose insulin and a delayed correct diagnosis and treatment, rendering substantial risk for the patient. Awareness of this dangerous interference is warranted.

Gepubliceerd: Cureus. 2022;14(8):e28615.
Impact factor: 0 ; Q NVT

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33. Assess and validate predictive performance of models for in-hospital mortality in COVID-19 patients: A retrospective cohort study in the Netherlands comparing the value of registry data with high-granular electronic health records

Vagliano I, Schut MC, Abu-Hanna A, Dongelmans DA, de Lange DW, Gommers D, Cremer OL, Bosman RJ, Rigter S, Wils EJ, Frenzel T, de Jong R, Peters MAA, Kamps MJA, Ramnarain D, Nowitzky R, Nooteboom F, de Ruijter W, Urlings-Strop LC, Smit EGM, Mehagnoul-Schipper DJ, Dormans T, de Jager CPC, Hendriks SHA, Achterberg S, Oostdijk E, Reidinga AC, Festen-Spanjer B, Brunnekreef GB, Cornet AD, van den Tempel W, Boelens AD, Koetsier P, Lens J, Faber HJ, Karakus A, Entjes R, de Jong P, Rettig TCD, Reuland MC, Arbous S, Fleuren LM, Dam TA, Thoral PJ, Lalisang RCA, Tonutti M, de Bruin DP, Elbers PWG, de Keizer NF.

Purpose: To assess, validate and compare the predictive performance of models for in-hospital mortality of COVID-19 patients admitted to the intensive care unit (ICU) over two different waves of infections. Our models were built with high-granular Electronic Health Records (EHR) data versus less-granular registry data**.**
Methods: Observational study of all COVID-19 patients admitted to 19 Dutch ICUs participating in both the national quality registry National Intensive Care Evaluation (NICE) and the EHR-based Dutch Data Warehouse (hereafter EHR). Multiple models were developed on data from the first 24 h of ICU admissions from February to June 2020 (first COVID-19 wave) and validated on prospective patients admitted to the same ICUs between July and December 2020 (second COVID-19 wave). We assessed model discrimination, calibration, and the degree of relatedness between development and validation population. Coefficients were used to identify relevant risk factors**.**
Results: A total of 1533 patients from the EHR and 1563 from the registry were included. With high granular EHR data, the average AUROC was 0.69 (standard deviation of 0.05) for the internal validation, and the AUROC was 0.75 for the temporal validation. The registry model achieved an average AUROC of 0.76 (standard deviation of 0.05) in the internal validation and 0.77 in the temporal validation. In the EHR data, age, and respiratory-system related variables were the most important risk factors identified. In the NICE registry data, age and chronic respiratory insufficiency were the most important risk factors**.**
Conclusion: In our study, prognostic models built on less-granular but readily-available registry data had similar performance to models built on high-granular EHR data and showed similar transportability to a prospective COVID-19 population. Future research is needed to verify whether this finding can be confirmed for upcoming waves.

Gepubliceerd: Int J Med Inform. 2022;167:104863.
Impact factor: 4.730 ; Q1

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34. C-Terminal Proarginine Vasopressin is Associated with Disease Outcome and Mortality, but not with Delayed Cerebral Ischemia in Critically Ill Patients with an Aneurysmal Subarachnoid Hemorrhage: A Prospective Cohort Study

van Oers JAH, Ramnarain D, Oldenbeuving A, Vos P, Roks G, Kluiters Y, Beishuizen A, de Lange DW, de Grooth HJ, Girbes ARJ.

Background: Aneurysmal subarachnoid hemorrhage (aSAH) is an important indication for intensive care unit admission and may lead to significant morbidity and mortality. We assessed the ability of C-terminal proarginine vasopressin (CT-proAVP) to predict disease outcome, mortality, and delayed cerebral ischemia (DCI) in critically ill patients with aSAH compared with the World Federation of Neurological Surgeons (WFNS) score and Acute Physiological and Chronic Health Evaluation IV (APACHE IV) model**.**

Methods: C-terminal proarginine vasopressin was collected on admission in this single-center, prospective, observational cohort study. The primary aim was to investigate the relationship between CT-proAVP and poor functional outcome at 1 year (Glasgow Outcome Scale score 1-3) in a multivariable logistic regression model adjusted for WFNS and APACHE IV scores. Secondary aims were mortality and DCI. The multivariable logistic regression model for DCI was also adjusted for the modified Fisher scale**.**
Results: In 100 patients, the median CT-proAVP level was 24.9 pmol/L (interquartile range 11.5-53.8); 45 patients had a poor 1-year functional outcome, 19 patients died within 30 days, 25 patients died within 1 year, and DCI occurred in 28 patients. Receiver operating characteristics curves revealed high accuracy for CT-proAVP to identify patients with poor 1-year functional outcome (area under the curve [AUC] 0.84, 95% confidence interval [CI] 0.77-0.92, p < 0.001), 30-day mortality (AUC 0.84, 95% CI 0.76-0.93, p < 0.001), and 1-year mortality (AUC 0.79, 95% CI 0.69-0.89, p < 0.001). CT-proAVP had a low AUC for identifying patients with DCI (AUC 0.67, 95% CI 0.55-0.79, p 0.008). CT-proAVP ≥ 24.9 pmo/L proved to be a significant predictor for poor 1-year functional outcome (odds ratio [OR] 8.04, 95% CI 2.97-21.75, p < 0.001), and CT-proAVP ≥ 29.1 pmol/L and ≥ 27.7 pmol/L were significant predictors for 30-day and 1-year mortality (OR 9.31, 95% CI 1.55-56.07, p 0.015 and OR 5.15, 95% CI 1.48-17.93, p 0.010) in multivariable models with WFNS and APACHE IV scores. CT-proAVP ≥ 29.5 pmol/L was not a significant predictor for DCI in a multivariable model adjusted for the modified Fisher scale (p = 0.061).
Conclusions: C-terminal proarginine vasopressin was able to predict poor functional outcome and mortality in critically ill patients with aSAH. Its prognostic ability to predict DCI was low.
Trial registration: Nederlands Trial Register: NTR4118.

Gepubliceerd: Neurocrit Care. 2022;37(3):678-88.
Impact factor: 3.532 ; Q2

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35. Anti-C5a antibody (vilobelimab) therapy for critically ill, invasively mechanically ventilated patients with COVID-19 (PANAMO): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial
Vlaar APJ, Witzenrath M, van Paassen P, Heunks LMA, Mourvillier B, de Bruin S, Lim EHT, Brouwer MC, Tuinman PR, Saraiva JFK, Marx G, Lobo SM, Boldo R, Simon-Campos JA, Cornet AD, Grebenyuk A, Engelbrecht JM, Mukansi M, Jorens PG, Zerbib R, Rückinger S, Pilz K, Guo R, van de Beek D, Riedemann NC.

Background: Vilobelimab, an anti-C5a monoclonal antibody, was shown to be safe in a phase 2 trial of invasively mechanically ventilated patients with COVID-19. Here, we aimed to determine whether vilobelimab in addition to standard of care improves survival outcomes in this patient population**.**
Methods: This randomised, double-blind, placebo-controlled, multicentre phase 3 trial was performed at 46 hospitals in the Netherlands, Germany, France, Belgium, Russia, Brazil, Peru, Mexico, and South Africa. Participants aged 18 years or older who were receiving invasive mechanical ventilation, but not more than 48 h after intubation at time of first infusion, had a PaO(2)/FiO(2) ratio of 60-200 mm Hg, and a confirmed SARS-CoV-2 infection with any variant in the past 14 days were eligible for this study. Eligible patients were randomly assigned (1:1) to receive standard of care and vilobelimab at a dose of 800 mg intravenously for a maximum of six doses (days 1, 2, 4, 8, 15, and 22) or standard of care and a matching placebo using permuted block randomisation. Treatment was not continued after hospital discharge. Participants, caregivers, and assessors were masked to group assignment. The primary outcome was defined as all-cause mortality at 28 days in the full analysis set (defined as all randomly assigned participants regardless of whether a patient started treatment, excluding patients randomly assigned in error) and measured using Kaplan-Meier analysis. Safety

analyses included all patients who had received at least one infusion of either vilobelimab or placebo. This study is registered with ClinicalTrials.gov, NCT04333420**.**
Findings: From Oct 1, 2020, to Oct 4, 2021, we included 368 patients in the ITT analysis (full analysis set; 177 in the vilobelimab group and 191 in the placebo group). One patient in the vilobelimab group was excluded from the primary analysis due to random assignment in error without treatment. At least one dose of study treatment was given to 364 (99%) patients (safety analysis set). 54 patients (31%) of 177 in the vilobelimab group and 77 patients (40%) of 191 in the placebo group died in the first 28 days. The all-cause mortality rate at 28 days was 32% (95% CI 25-39) in the vilobelimab group and 42% (35-49) in the placebo group (hazard ratio 0·73, 95% CI 0·50-1·06; p=0·094). In the predefined analysis without site-stratification, vilobelimab significantly reduced all-cause mortality at 28 days (HR 0·67, 95% CI 0·48-0·96; p=0·027). The most common TEAEs were acute kidney injury (35 [20%] of 175 in the vilobelimab group vs 40 [21%] of 189 in the placebo), pneumonia (38 [22%] vs 26 [14%]), and septic shock (24 [14%] vs 31 [16%]). Serious treatment-emergent adverse events were reported in 103 (59%) of 175 patients in the vilobelimab group versus 120 (63%) of 189 in the placebo group.
Interpretation: In addition to standard of care, vilobelimab improves survival of invasive mechanically ventilated patients with COVID-19 and leads to a significant decrease in mortality. Vilobelimab could be considered as an additional therapy for patients in this setting and further research is needed on the role of vilobelimab and C5a in other acute respiratory distress syndrome-causing viral infections. FUNDING: InflaRx and the German Federal Government.

Gepubliceerd: Lancet Respir Med. 2022;10(12):1137-46.
Impact factor: 102.642 ; Q1

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36. Paediatric COVID-19 mortality: a database analysis of the impact of health resource disparity
Marwali EM, Kekalih A, Yuliarto S, Wati DK, Rayhan M, Valerie IC, Cho HJ, Jassat W, Blumberg L, Masha M, Semple C, Swann OV, Kohns Vasconcelos M, Popielska J, Murthy S, Fowler RA, Guerguerian AM, Streinu-Cercel A, Pathmanathan MD, Rojek A, Kartsonaki C, Goncalves BP, Citarella BW, Merson L, Olliaro PL, Dalton HJ, International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Clinical Characterization Group Investigators; Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H

Background: The impact of the COVID-19 pandemic on paediatric populations varied between high-income countries (HICs) versus low-income to middle-income countries (LMICs). We sought to investigate differences in paediatric clinical outcomes and identify factors contributing to disparity between countries.
Methods: The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) COVID-19 database was queried to include children under 19 years of age admitted to hospital from January 2020 to April 2021 with suspected or confirmed COVID-19 diagnosis. Univariate and multivariable analysis of contributing factors for mortality were assessed by country group (HICs vs LMICs) as defined by the World Bank criteria.
Results: A total of 12 860 children (3819 from 21 HICs and 9041 from 15 LMICs) participated in this study. Of these, 8961 were laboratory-confirmed and 3899 suspected COVID-19 cases. About 52% of LMICs children were black, and more than 40% were infants and adolescent. Overall in-hospital mortality rate (95% CI) was 3.3% [=(3.0% to 3.6%), higher in LMICs than HICs (4.0% (3.6% to 4.4%) and 1.7% (1.3% to 2.1%), respectively). There were significant differences between country income groups in intervention profile, with higher use of antibiotics, antivirals, corticosteroids, prone positioning, high flow nasal cannula, non-invasive and invasive mechanical ventilation in HICs. Out of the 439 mechanically ventilated children, mortality occurred in 106 (24.1%) subjects, which was higher in LMICs than HICs (89 (43.6%) vs 17 (7.2%) respectively). Pre-existing infectious comorbidities

(tuberculosis and HIV) and some complications (bacterial pneumonia, acute respiratory distress syndrome and myocarditis) were significantly higher in LMICs compared with HICs. On multivariable analysis, LMIC as country income group was associated with increased risk of mortality (adjusted HR 4.73 (3.16 to 7.10)).
Conclusion: Mortality and morbidities were higher in LMICs than HICs, and it may be attributable to differences in patient demographics, complications and access to supportive and treatment modalities.

Gepubliceerd: BMJ Paediatr Open. 2022;6(1).
Impact factor: 2.922; Q2

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37. Treating Rhythmic and Periodic EEG Patterns in Comatose Survivors of Cardiac Arrest
Ruijter BJ, Keijzer HM, Tjepkema-Cloostermans MC, Blans MJ, Beishuizen A, Tromp SC, Scholten E, Horn J, van Rootselaar AF, Admiraal MM, van den Bergh WM, Elting JJ, Foudraine NA, Kornips FHM, van Kranen-Mastenbroek V, Rouhl RPW, Thomeer EC, Moudrous W, Nijhuis FAP, Booij SJ, Hoedemaekers CWE, Doorduin J, Taccone FS, van der Palen J, van Putten M, Hofmeijer J, Telstar Investigators.

Background: Whether the treatment of rhythmic and periodic electroencephalographic (EEG) patterns in comatose survivors of cardiac arrest improves outcomes is uncertain.
Methods: We conducted an open-label trial of suppressing rhythmic and periodic EEG patterns detected on continuous EEG monitoring in comatose survivors of cardiac arrest. Patients were randomly assigned in a 1:1 ratio to a stepwise strategy of antiseizure medications to suppress this activity for at least 48 consecutive hours plus standard care (antiseizure-treatment group) or to standard care alone (control group); standard care included targeted temperature management in both groups. The primary outcome was neurologic outcome according to the score on the Cerebral Performance Category (CPC) scale at 3 months, dichotomized as a good outcome (CPC score indicating no, mild, or moderate disability) or a poor outcome (CPC score indicating severe disability, coma, or death). Secondary outcomes were mortality, length of stay in the intensive care unit (ICU), and duration of mechanical ventilation.
Results: We enrolled 172 patients, with 88 assigned to the antiseizure-treatment group and 84 to the control group. Rhythmic or periodic EEG activity was detected a median of 35 hours after cardiac arrest; 98 of 157 patients (62%) with available data had myoclonus. Complete suppression of rhythmic and periodic EEG activity for 48 consecutive hours occurred in 49 of 88 patients (56%) in the antiseizure-treatment group and in 2 of 83 patients (2%) in the control group. At 3 months, 79 of 88 patients (90%) in the antiseizure-treatment group and 77 of 84 patients (92%) in the control group had a poor outcome (difference, 2 percentage points; 95% confidence interval, -7 to 11; P = 0.68). Mortality at 3 months was 80% in the antiseizure-treatment group and 82% in the control group. The mean length of stay in the ICU and mean duration of mechanical ventilation were slightly longer in the antiseizure-treatment group than in the control group.
Conclusions: In comatose survivors of cardiac arrest, the incidence of a poor neurologic outcome at 3 months did not differ significantly between a strategy of suppressing rhythmic and periodic EEG activity with the use of antiseizure medication for at least 48 hours plus standard care and standard care alone.
(Funded by the Dutch Epilepsy Foundation; TELSTAR ClinicalTrials.gov number, NCT02056236.).

Gepubliceerd: N Engl J Med. 2022;386(8):724-34.
Impact factor: 176.082 ; Q1

Totale impact factor: 646.581
Gemiddelde impact factor: 17.475

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 2.150
Gemiddelde impact factor: 2.150

Interne geneeskunde

1. Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With High Risk for Postoperative Complications: Results of a Randomized Clinical Trial
Berkel AEM, Bongers BC, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, Wymenga M, Bigirwamungu-Bargeman M, van der Palen J, van Det MJ, van Meeteren NLU, Klaase JM.

Objective: To assess the effects of a 3-week community-based exercise program on 30-day postoperative complications in high-risk patients scheduled for elective colorectal resection for (pre)malignancy.
Summary Background data: Patients with a low preoperative aerobic fitness undergoing colorectal surgery have an increased risk of postoperative complications. It remains, however, to be demonstrated whether prehabilitation in these patients reduces postoperative complications**.**
Methods: This 2-center, prospective, single-blinded randomized clinical trial was carried out in 2 large teaching hospitals in the Netherlands. Patients (≥60 years) with colorectal (pre)malignancy scheduled for elective colorectal resection and with a score ≤7 metabolic equivalents on the veterans-specific activity questionnaire were randomly assigned to the prehabilitation group or the usual care group by using block-stratified randomization. An oxygen uptake at the ventilatory anaerobic threshold <11 mL/kg/min at the baseline cardiopulmonary exercise test was the final inclusion criterion. Inclusion was based on a power analysis. Patients in the prehabilitation group participated in a personalized 3-week (3 sessions per week, nine sessions in total) supervised exercise program given in community physical therapy practices before colorectal resection. Patients in the reference group received usual care. The primary outcome was the number of patients with one or more complications within 30 days of surgery, graded according to the Clavien-Dindo classification. Data were analyzed on an intention-to-treat basis**.**
Results: Between February 2014 and December 2018, 57 patients [30 males and 27 females; mean age 73.6 years (standard deviation 6.1), range 61-88 years] were randomized to either prehabilitation (n = 28) or usual care (n = 29). The rate of postoperative complications was lower in the prehabilitation group (n = 12, 42.9%) than in the usual care group (n = 21, 72.4%, relative risk 0.59, 95% confidence interval 0.37-0.96, P = 0.024).
Conclusions: Exercise prehabilitation reduced postoperative complications in high-risk patients scheduled to undergo elective colon resection for (pre)malignancy. Prehabilitation should be considered as usual care in high-risk patients scheduled for elective colon, and probably also rectal, surgery.

Gepubliceerd: Ann Surg. 2022;275(2):e299-e306.
Impact factor: 13.787 ; Q1

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2. Increased mortality risk in multiple-myeloma patients with subsequent malignancies: a population-based study in the Netherlands
Brink M, Minnema MC, Visser O, Levin MD, Posthuma E, Broijl A, Sonneveld P, van der Klift M, Roeloffzen WWH, Westerman M, van Rooijen CR, Geerts PAF, Zweegman S, van de Donk N, Dinmohamed AG.

Gepubliceerd: Blood Cancer J. 2022;12(3):41.
Impact factor: 9.812 ; Q1

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3. Cross-linguistic influence in simultaneous and early sequential bilingual children: a meta-analysis

Van Dijk C, van Wonderen E, Koutamanis E, Kootstra GJ, Dijkstra T, Unsworth S.

Although cross-linguistic influence at the level of morphosyntax is one of the most intensively studied topics in child bilingualism, the circumstances under which it occurs remain unclear. In this meta-analysis, we measured the effect size of cross-linguistic influence and systematically assessed its predictors in 750 simultaneous and early sequential bilingual children in 17 unique language combinations across 26 experimental studies. We found a significant small to moderate average effect size of cross-linguistic influence, indicating that cross-linguistic influence is part and parcel of bilingual development. Language dominance, operationalized as societal language, was a significant predictor of cross-linguistic influence, whereas surface overlap, language domain and age were not. Perhaps an even more important finding was that definitions and operationalisations of cross-linguistic influence and its predictors varied considerably between studies. This could explain the absence of a comprehensive theory in the field. To solve this issue, we argue for a more uniform method of studying cross-linguistic influence.

Gepubliceerd: J Child Lang. 2022;49(5):897-929.
Impact factor: 2.701 ; Q1

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4. Harmonising patient-access programmes: the Dutch DRUG Access Protocol platform
Zeverijn LJ, van Waalwijk van Doorn-Khosrovani SB, van Roy A, Timmers L, Ly Tran TH, de Boer JE, de Wit GF, Geurts BS, Gelderblom H, Verheul HMW, Blijlevens N, Wymenga ANM, Eskens F, Smit EF, Bloemendal HJ, Voest EE.

Gepubliceerd: Lancet Oncol. 2022;23(2):198-201.
Impact factor: 54.433 ; Q1

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5. Assessment of new oncological drugs
Wymenga ANM.

As the number of cancer patients increases and new (mostly expensive) treatment options are evolving rapidly, a critical evaluation of the value of new treatments is required in order to maintain access to new drugs and affordable cancer care. In the Netherlands, the Dutch Society of Medical Oncology- CieBOM (NVMO CieBOM) has an unique role in assessment of the value and use of new oncological drugs, next to the National Committee of Health Insurance (cieBAG) and the Dutch Health Care Institute. CieBOM developed transparent criteria for approval of oncological drugs in several settings, and recently also criteria for drugs only tested in non-randomised studies have been developed.

Gepubliceerd: Ned Tijdschr Geneeskd. 2022;166.
Impact factor: 0 ; Q NVT

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6. A highly virulent variant of HIV-1 circulating in the Netherlands
Wymant C, Bezemer D, Blanquart F, Ferretti L, Gall A, Hall M, Golubchik T, Bakker M, Ong SH, Zhao L, Bonsall D, de Cesare M, MacIntyre-Cockett G, Abeler-Dörner L, Albert J, Bannert N, Fellay J, Grabowski MK, Gunsenheimer-Bartmeyer B, Günthard HF, Kivelä P, Kouyos RD, Laeyendecker O, Meyer L, Porter K, Ristola M, van Sighem A, Berkhout B, Kellam P, Cornelissen M, Reiss P, Fraser C, Netherlands ATHENA HIV Observational Cohort†; BEEHIVE Collaboration†; Kootstra GJ.

We discovered a highly virulent variant of subtype-B HIV-1 in the Netherlands. One hundred nine individuals with this variant had a 0.54 to 0.74 log(10) increase (i.e., a ~3.5-fold to 5.5-fold increase) in viral load compared with, and exhibited CD4 cell decline twice as fast as, 6604 individuals with other subtype-B strains. Without treatment, advanced HIV-CD4 cell counts below 350 cells per cubic millimeter, with long-term clinical consequences-is expected to be reached, on average, 9 months after diagnosis for individuals in their thirties with this variant. Age, sex, suspected mode of transmission, and place of birth for the aforementioned 109 individuals were typical for HIV-positive people in the Netherlands, which suggests that the increased virulence is attributable to the viral strain. Genetic sequence analysis suggests that this variant arose in the 1990s from de novo mutation, not recombination, with increased transmissibility and an unfamiliar molecular mechanism of virulence.

Gepubliceerd: Science. 2022;375(6580):540-5.
Impact factor: 63.832 ; Q1

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7. ISARIC-COVID-19 dataset: A Prospective, Standardized, Global Dataset of Patients Hospitalized with COVID-19
Garcia-Gallo E, Merson L, Kennon K, Kelly S, Citarella BW, Fryer DV, Shrapnel S, Lee J, Duque S, Fuentes YV, Balan V, Smith S, Wei J, Gonçalves BP, Russell CD, Sigfrid L, Dagens A, Olliaro PL, Baruch J, Kartsonaki C, Dunning J, Rojek A, Rashan A, Beane A, Murthy S, Reyes LF, ISARIC Clinical Characterization Group: Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H.

The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) COVID-19 dataset is one of the largest international databases of prospectively collected clinical data on people hospitalized with COVID-19. This dataset was compiled during the COVID-19 pandemic by a network of hospitals that collect data using the ISARIC-World Health Organization Clinical Characterization Protocol and data tools. The database includes data from more than 705,000 patients, collected in more than 60 countries and 1,500 centres worldwide. Patient data are available from acute hospital admissions with COVID-19 and outpatient follow-ups. The data include signs and symptoms, pre-existing comorbidities, vital signs, chronic and acute treatments, complications, dates of hospitalization and discharge, mortality, viral strains, vaccination status, and other data. Here, we present the dataset characteristics, explain its architecture and how to gain access, and provide tools to facilitate its use.

Gepubliceerd: Sci Data. 2022;9(1):454.
Impact factor: 8.501 ; Q1

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8. Effectiveness and implementation of SHared decision-making supported by OUTcome information among patients with breast cancer, stroke and advanced kidney disease: SHOUT study protocol of multiple interrupted time series
Hackert MQN, Ankersmid JW, Engels N, Prick JCM, Teerenstra S, Siesling S, Drossaert CHC, Strobbe LJA, van Riet YEA, van den Dorpel RMA, Bos WJW, van der Nat PB, van den Berg-Vos RM, van Schaik SM, Garvelink MM, van der Wees PJ, van Uden-Kraan CF, Santeon VBHC breast cancer, stroke and chronic kidney disease group; Brinkman JN, Brouwers PJAM, Dassen AE.

Introduction: Within the value-based healthcare framework, outcome data can be used to inform patients about (treatment) options, and empower them to make shared decisions with their health care professional. To facilitate shared decision-making (SDM) supported by outcome data, a

multicomponent intervention has been designed, including patient decision aids on the organisation of post-treatment surveillance (breast cancer); discharge location (stroke) and treatment modality (advanced kidney disease), and training on SDM for health care professionals. The SHared decision-making supported by OUTcome information (SHOUT) study will examine the effectiveness of the intervention and its implementation in clinical practice.
Methods and Analysis: Multiple interrupted time series will be used to stepwise implement the intervention. Patients diagnosed with either breast cancer (N=630), stroke (N=630) or advanced kidney disease (N=473) will be included. Measurements will be performed at baseline, three (stroke), six and twelve (breast cancer and advanced kidney disease) months. Trends on outcomes will be measured over a period of 20 months. The primary outcome will be patients' perceived level of involvement in decision-making. Secondary outcomes regarding effectiveness will include patient-reported SDM, decisional conflict, role in decision-making, knowledge, quality of life, preferred and chosen care, satisfaction with the intervention, healthcare utilisation and health outcomes. Outcomes regarding implementation will include the implementation rate and a questionnaire on the health care professionals' perspective on the implementation process.
Ethics and Dissemination: The Medical research Ethics Committees United in Nieuwegein, the Netherlands, has confirmed that the Medical Research Involving Human Subjects Act does not apply to this study. Bureau Onderzoek & Innovatie of Santeon, the Netherlands, approved this study. The results will contribute to insight in and knowledge on the use of outcome data for SDM, and can stimulate sustainable implementation of SDM.
Trial registration number: NL8374, NL8375 and NL8376.

Gepubliceerd: BMJ Open. 2022;12(8):e055324.
Impact factor: 3.007; Q2

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9. Clinical presentation, disease course, and outcome of COVID-19 in hospitalized patients with and without pre-existing cardiac disease: a cohort study across 18 countries
CAPACITY-COVID Collaborative Consortium and LEOSS Study Group; Delsing CE, Meijs MFL, van Veen H, Vonkeman HE.

Aims: Patients with cardiac disease are considered high risk for poor outcomes following hospitalization with COVID-19. The primary aim of this study was to evaluate heterogeneity in associations between various heart disease subtypes and in-hospital mortality**.**
Methods and Results: We used data from the CAPACITY-COVID registry and LEOSS study. Multivariable Poisson regression models were fitted to assess the association between different types of pre-existing heart disease and in-hospital mortality. A total of 16 511 patients with COVID-19 were included (21.1% aged 66-75 years; 40.2% female) and 31.5% had a history of heart disease. Patients with heart disease were older, predominantly male, and often had other comorbid conditions when compared with those without. Mortality was higher in patients with cardiac disease (29.7%; n = 1545 vs. 15.9%; n = 1797). However, following multivariable adjustment, this difference was not significant [adjusted risk ratio (aRR) 1.08, 95% confidence interval (CI) 1.02-1.15; P = 0.12 (corrected for multiple testing)]. Associations with in-hospital mortality by heart disease subtypes differed considerably, with the strongest association for heart failure (aRR 1.19, 95% CI 1.10-1.30; P < 0.018) particularly for severe (New York Heart Association class III/IV) heart failure (aRR 1.41, 95% CI 1.20-1.64; P < 0.018). None of the other heart disease subtypes, including ischaemic heart disease, remained significant after multivariable adjustment. Serious cardiac complications were diagnosed in <1% of patients**.**
Conclusion: Considerable heterogeneity exists in the strength of association between heart disease subtypes and in-hospital mortality. Of all patients with heart disease, those with heart failure are at

greatest risk of death when hospitalized with COVID-19. Serious cardiac complications are rare during hospitalization.

Gepubliceerd: Eur Heart J. 2022;43(11):1104-20.
Impact factor: 35.855 ; Q1

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10. Optimising Access Surgery in Senior Haemodialysis Patients (OASIS): study protocol for a multicentre randomised controlled trial
Heggen BD, Ramspek CL, van der Bogt KEA, de Haan MW, Hemmelder MH, Hiligsmann MJC, van Loon MM, Rotmans JI, Tordoir JHM, Dekker FW, Schurink GWH, Snoeijs MGJ, Oasis Study Group: Brink HS, Willigendael EM.

Introduction: Current evidence on vascular access strategies for haemodialysis patients is based on observational studies that are at high risk of selection bias. For elderly patients, autologous arteriovenous fistulas that are typically created in usual care may not be the best option because a significant proportion of fistulas either fail to mature or remain unused. In addition, long-term complications associated with arteriovenous grafts and central venous catheters may be less relevant when considering the limited life expectancy of these patients. Therefore, we designed the Optimising Access Surgery in Senior Haemodialysis Patients (OASIS) trial to determine the best strategy for vascular access creation in elderly haemodialysis patients.
Methods and Analysis: OASIS is a multicentre randomised controlled trial with an equal participant allocation in three treatment arms. Patients aged 70 years or older who are expected to initiate haemodialysis treatment in the next 6 months or who have started haemodialysis urgently with a catheter will be enrolled. To detect and exclude patients with an unusually long life expectancy, we will use a previously published mortality prediction model after external validation. Participants allocated to the usual care arm will be treated according to current guidelines on vascular access creation and will undergo fistula creation. Participants allocated to one of the two intervention arms will undergo graft placement or catheter insertion. The primary outcome is the number of access-related interventions required for each patient-year of haemodialysis treatment. We will enrol 195 patients to have sufficient statistical power to detect an absolute decrease of 0.80 interventions per year.
Ethics and Dissemination: Because of clinical equipoise, we believe it is justified to randomly allocate elderly patients to the different vascular access strategies. The study was approved by an accredited medical ethics review committee. The results will be disseminated through peer-reviewed publications and will be implemented in clinical practice guidelines.
Trial registration number: NL7933. PROTOCOL VERSION AND DATE: V.5, 25 February 2021.

Gepubliceerd: BMJ Open. 2022;12(2):e053108.
Impact factor: 3.007; Q2

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11. Age is the main determinant of COVID-19 related in-hospital mortality with minimal impact of pre-existing comorbidities, a retrospective cohort study
Henkens M, Raafs AG, Verdonschot JAJ, Linschoten M, van Smeden M, Wang P, van der Hooft BHM, Tieleman R, Janssen MLF, Ter Bekke RMA, Hazebroek MR, van der Horst ICC, Asselbergs FW, Magdelijns FJH, Heymans SRB, CAPACITY-COVID Collaborative Consortium; Delsing CE, Meijs MFL, van Veen, Vonkeman HE.

Background: Age and comorbidities increase COVID-19 related in-hospital mortality risk, but the extent by which comorbidities mediate the impact of age remains unknown**.**

Methods: In this multicenter retrospective cohort study with data from 45 Dutch hospitals, 4806 proven COVID-19 patients hospitalized in Dutch hospitals (between February and July 2020) from the CAPACITY-COVID registry were included (age 69[58-77]years, 64% men). The primary outcome was defined as a combination of in-hospital mortality or discharge with palliative care. Logistic regression analysis was performed to analyze the associations between sex, age, and comorbidities with the primary outcome. The effect of comorbidities on the relation of age with the primary outcome was evaluated using mediation analysis**.**
Results: In-hospital COVID-19 related mortality occurred in 1108 (23%) patients, 836 (76%) were aged ≥70 years (70+). Both age 70+ and female sex were univariably associated with outcome (odds ratio [OR]4.68, 95%confidence interval [4.02-5.45], OR0.68[0.59-0.79], respectively;both p< 0.001). All comorbidities were univariably associated with outcome (p<0.001), and all but dyslipidemia remained significant after adjustment for age70+ and sex. The impact of comorbidities was attenuated after age-spline adjustment, only leaving female sex, diabetes mellitus (DM), chronic kidney disease (CKD), and chronic pulmonary obstructive disease (COPD) significantly associated (female OR0.65[0.55-0.75], DM OR1.47[1.26-1.72], CKD OR1.61[1.32-1.97], COPD OR1.30[1.07-1.59]). Pre-existing comorbidities in older patients negligibly (<6% in all comorbidities) mediated the association between higher age and outcome.
Conclusions: Age is the main determinant of COVID-19 related in-hospital mortality, with negligible mediation effect of pre-existing comorbidities.
Trial registration: CAPACITY-COVID (NCT04325412).

Gepubliceerd: BMC Geriatr. 2022;22(1):184.
Impact factor: 4.070 ; Q2

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12. Immunogenicity and reactogenicity of SARS-CoV-2 vaccines in people living with HIV in the Netherlands: A nationwide prospective cohort study
Hensley KS, Jongkees MJ, Geers D, GeurtsvanKessel CH, Mueller YM, Dalm V, Papageorgiou G, Steggink H, Gorska A, Bogers S, den Hollander JG, Bierman WFW, Gelinck LBS, Schippers EF, Ammerlaan HSM, van der Valk M, van Vonderen MGA, Delsing CE, Gisolf EH, Bruns AHW, Lauw FN, Berrevoets MAH, Sigaloff KCE, Soetekouw R, Branger J, de Mast Q, Lammers AJJ, Lowe SH, de Vries RD, Katsikis PD, Rijnders BJA, Brinkman K, Roukens AHE, Rokx C.

Background: Vaccines can be less immunogenic in people living with HIV (PLWH), but for SARS-CoV-2 vaccinations this is unknown. In this study we set out to investigate, for the vaccines currently approved in the Netherlands, the immunogenicity and reactogenicity of SARS-CoV-2 vaccinations in PLWH.
Methods and findings: We conducted a prospective cohort study to examine the immunogenicity of BNT162b2, mRNA-1273, ChAdOx1-S, and Ad26.COV2.S vaccines in adult PLWH without prior COVID-19, and compared to HIV-negative controls. The primary endpoint was the anti-spike SARS-CoV-2 IgG response after mRNA vaccination. Secondary endpoints included the serological response after vector vaccination, anti-SARS-CoV-2 T-cell response, and reactogenicity. Between 14 February and 7 September 2021, 1,154 PLWH (median age 53 [IQR 44-60] years, 85.5% male) and 440 controls (median age 43 [IQR 33-53] years, 28.6% male) were included in the final analysis. Of the PLWH, 884 received BNT162b2, 100 received mRNA-1273, 150 received ChAdOx1-S, and 20 received Ad26.COV2.S. In the group of PLWH, 99% were on antiretroviral therapy, 97.7% were virally suppressed, and the median CD4+ T-cell count was 710 cells/μL (IQR 520-913). Of the controls, 247 received mRNA-1273, 94 received BNT162b2, 26 received ChAdOx1-S, and 73 received Ad26.COV2.S. After mRNA vaccination, geometric mean antibody concentration was 1,418 BAU/mL in PLWH (95% CI 1322-1523), and after adjustment for age, sex, and vaccine type, HIV status remained associated with a decreased response (0.607, 95% CI 0.508-0.725, p < 0.001). All controls receiving an mRNA

vaccine had an adequate response, defined as >300 BAU/mL, whilst in PLWH this response rate was 93.6%. In PLWH vaccinated with mRNA-based vaccines, higher antibody responses were predicted by CD4+ T-cell count 250-500 cells/μL (2.845, 95% CI 1.876-4.314, p < 0.001) or >500 cells/μL (2.936, 95% CI 1.961-4.394, p < 0.001), whilst a viral load > 50 copies/mL was associated with a reduced response (0.454, 95% CI 0.286-0.720, p = 0.001). Increased IFN-γ, CD4+ T-cell, and CD8+ T-cell responses were observed after stimulation with SARS-CoV-2 spike peptides in ELISpot and activation-induced marker assays, comparable to controls. Reactogenicity was generally mild, without vaccine-related serious adverse events. Due to the control of vaccine provision by the Dutch National Institute for Public Health and the Environment, there were some differences between vaccine groups in the age, sex, and CD4+ T-cell counts of recipients.
Conclusions: After vaccination with BNT162b2 or mRNA-1273, anti-spike SARS-CoV-2 antibody levels were reduced in PLWH compared to HIV-negative controls. To reach and maintain the same serological responses as HIV-negative controls, additional vaccinations are probably required.
Trial registration: The trial was registered in the Netherlands Trial Register (NL9214). https://www.trialregister.nl/trial/9214.

Gepubliceerd: PLoS Med. 2022;19(10):e1003979.
Impact factor: 11.613 ; Q1

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13. Long-term survival of patients with advanced melanoma treated with BRAF-MEK inhibitors
Ismail RK, Suijkerbuijk KPM, de Boer A, van Dartel M, Hilarius DL, Pasmooij AMG, van Zeijl MCT, Aarts MJB, van den Berkmortel F, Blank CU, Boers-Sonderen MJ, de Groot JWB, Haanen J, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, van der Veldt AAM, Vreugdenhil A, Westgeest H, van den Eertwegh AJ, Wouters M.

Recent results of patients with advanced melanoma treated with first-line BRAF-MEK inhibitors in clinical trials showed 5-year survival in one-third of patients with a median overall survival (OS) of more than 2 years. This study aimed to investigate these patients' real-world survival and identify the characteristics of long-term survivors. The study population consisted of patients with advanced cutaneous melanoma with a BRAF-V600 mutated tumor who were treated with first-line BRAF-MEK inhibitors between 2013 and 2017. Long-term survival was defined as a minimum OS of 2 years from start therapy. The median progression-free survival (mPFS) and median OS (mOS) of real-world patients (n = 435) were respectively 8.0 (95% CI, 6.8-9.4) and 11.7 (95% CI, 10.3-13.5) months. Two-year survival was reached by 28% of the patients, 22% reached 3-year survival and 19% reached 4-year survival. Real-world patients often had brain metastases (41%), stage IV M1c disease (87%), ECOG PS ≥2 (21%), ≥3 organ sites (62%) and elevated LDH of ≥250 U/l (49%). Trial-eligible real-world patients had an mOS of 17.9 months. Patients surviving more than 2 years (n = 116) more often had an ECOG PS ≤1 (83%), normal LDH (60%), no brain metastases (60%), no liver metastases (63%) and <3 organ sites (60%). Long-term survival of real-world patients treated with first-line BRAF-MEK inhibitors is significantly lower than that of trial patients, which is probably explained by poorer baseline characteristics of patients treated in daily practice. Long-term survivors generally had more favorable characteristics with regard to age, LDH level and metastatic sites, compared to patients not reaching long-term survival.

Gepubliceerd: Melanoma Res. 2022;32(6):460-8.
Impact factor: 3.199 ; Q2

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14. Addition of the nuclear export inhibitor selinexor to standard intensive treatment for elderly patients with acute myeloid leukemia and high risk myelodysplastic syndrome

Janssen J, Löwenberg B, Manz M, Biemond BJ, Westerweel PE, Klein SK, Fehr M, Sinnige HAM, Efthymiou A, Legdeur M, Pabst T, Gregor M, van der Poel MWM, Deeren D, Tick LW, Jongen-Lavrencic M, van Obbergh F, Boersma RS, de Weerdt O, Chalandon Y, Heim D, Spertini O, van Sluis G, Graux C, Stüssi G, van Norden Y, Ossenkoppele GJ.

Treatment results of AML in elderly patients are unsatisfactory. In an open label randomized phase II study, we investigated whether addition of the XPO1 inhibitor selinexor to intensive chemotherapy would improve outcome in this population. 102 AML patients > 65 years of age (median 69 (65-80)) were randomly assigned to standard chemotherapy (3 + 7) with or without oral selinexor 60 mg twice weekly (both arms n = 51), days 1-24. In the second cycle, cytarabine 1000 mg/m(2) twice daily, days 1-6 with or without selinexor was given. CR/CRi rates were significantly higher in the control arm than in the investigational arm (80% (95% C.I. 69-91%) vs. 59% (45-72%; p = 0.018), respectively). At 18 months, event-free survival was 45% for the control arm versus 26% for the investigational arm (Cox-p = 0.012) and overall survival 58% vs. 33%, respectively (p = 0.009). AML and infectious complications accounted for an increased death rate in the investigational arm. Irrespective of treatment, MRD status after two cycles appeared to be correlated with survival. We conclude that the addition of selinexor to standard chemotherapy does negatively affect the therapeutic outcome of elderly AML patients. (Netherlands Trial Registry number NL5748 (NTR5902), www.trialregister.nl).

Gepubliceerd: Leukemia. 2022;36(9):2189-95.
Impact factor: 12.897 ; Q1

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15. Lenalidomide-Rituximab or Lenalidomide-Rituximab-Bendamustine in Patients with Relapsed/Refractory Follicular Lymphoma: Priimary Analysis of the Randomized Phase II HOVON110/Rebel Trial

Kersten MJ, Dreyling M, Linton KM, Chitu D, Tonino S, Kap M, Liu RD, Chamuleau MED, Visser HPJ, De Jongh E, Marijt EW, Leijs MBL, Bilgin YM, Dürig J, McKay P, Snijders TJF, Pettitt A, Minnema MC, Prange-Krex G, Cuijpers M, Böhmer LH, Tick LW, Florschütz A, Silbermann M, Fijnheer R, Beeker A, Tolboom N, Mitea C, Arens AI, Zwezerijnen GJ, Klapper W, Coupland SE, de Jong D, Doorduijn JK, Zijlstra JM.

Introduction: The R2 regimen (lenalidomide-rituximab) is effective in treatment-naive and relapsed/refractory follicular lymphoma (R/R FL). Combining R2 with bendamustine (R2B) is feasible (Stevens WBC et al., Hemasphere 2020) and hypothesized to deepen remission and prolong event-free survival (EFS) compared to historic controls. We performed a randomized phase II trial of R2 and R2B, aiming at identifying the most promising arm to take forward to a randomized phase III trial.
Methods: In the multicenter, prospective, randomized, non-comparative phase II part of the HOVON110/ReBeL study (Dutch Clinical Trial Register NTR3028), patients (pts) with FL relapsed after ≤5 prior therapies were randomized 1:1 to R2 (Arm A) or R2B (Arm B). Stratification factors used were FLIPI score (0-2 vs 3-5), number of prior treatments (1 vs 2-5), prior bendamustine use and relapse during rituximab maintenance (RM). Arm A pts received 6 cycles of R2 q28 days (lenalidomide 20 mg day 1-21, rituximab 375 mg/m2 day 1); Arm B pts received 6 cycles of R2B q28 days (lenalidomide 20 mg day 3-21, rituximab 375 mg/m2 day 1, bendamustine 90 mg/m2 day 1,2). In both arms, pts with partial or complete remission (PR/CR) received 2 years of RM treatment, once every three months. Subcutaneous rituximab was allowed. Thrombosis prophylaxis was advised during induction; antimicrobial prophylaxis with valaciclovir and cotrimoxazole was mandatory in arm B. Arms A and B were separately evaluated for efficacy and toxicity. Co-primary endpoints were CT-based CR rate according to Cheson 2007 criteria at end of induction (EOI) and incidence of severe toxicities (ST), defined as grade ≥ 3 non-hematological toxicity, specified grade 4 hematologic toxicity

(neutropenia lasting ≥ 7 days despite GCSF, febrile neutropenia, thrombocytopenia) or non-lymphoma related death. An event for event-free survival was defined as induction failure, progression, relapse or death from any cause. PET-CT was performed before and after induction. Central pathology and blinded central PET-CT review (Lugano classification) were performed.
Results: Between 2014 and 2019, 92 of 150 planned pts were randomized. The trial was stopped early because of slow accrual. Two pts (1 in each arm) were ineligible. Baseline characteristics were comparable between Arms A/B in terms of gender and median age (64/62 years). Most pts had stage III/IV disease (85%/80%), an intermediate/high risk FLIPI score (78%/89%) and had undergone 1 prior treatment (75%/76%; range 1-5).
For pts in arms A/B, 80%/76% completed all 6 induction cycles and 41%/43% completed 8 cycles of RM. Main reasons for discontinuation during induction were progressive disease (PD) (n=4 per arm) and toxicity or other reasons in 5/7 patients. Severe toxicity (ST) occurred in 3 pts in arm A (6.8%; 2 fatal pneumonia cases) and in 6 pts in arm B (13.0%; no fatalities), while 43%/66% of pts experienced any grade 3-4 AE (2%/7% grade 4). These comprised mainly skin toxicity, infections and gastrointestinal toxicity. In the R2B arm, 1 pt had Pneumocystis carinii pneumonia during RM.
Based on intention to treat (ITT) and local CT assessment (efficacy co-primary endpoint), 16% of R2 and 22% of R2B treated pts achieved a CR at EOI; the overall response rate (ORR) was 70% and 72%, respectively. The complete metabolic remission rate (CMR) by central PET-CT review at EOI was 48% and 54%. At a median follow-up of 48 months (mo), EFS was 39% and 61%; median EFS was 24.6 mo and not reached (NR). Importantly, median time to next treatment (TTnT) was 9.2 mo and NR. There were 7 second primary malignancies (SPM) in 5 pts in Arm A) and 5 SPM in 4 pts in Arm B). Overall survival was excellent in both arms with 72% and 91% of pts alive at 48 months. Causes of death during the study were progression of FL (n=8) and toxicity (n=3) in Arm A; FL (n=3), toxicity (n=1) and suicide (n=1) in Arm B.
Conclusions: This randomized non-comparative phase II trial of R2 and R2B in R/R FL patients showed high CT-based OR rates and PET-CT CMR rates, but low CT-based CR rates for both treatments. At a median FU of 48 months, 39% of R2 treated patients and 61% of R2B treated patients were still alive and in remission; this compares favorably with historic real world controls (Batlevi et al, Blood Cancer J 2020). Both regimens were associated with less severe toxicity than expected (pre-set acceptability threshold of 20% ST), supporting further investigation of R2 combinations in randomized phase III trials.

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Impact factor: 22.669 ; Q1

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16. Transplant, treatment and transfusion free (TTT-free) survival as relevant clinical endpoint after immunosuppressive treatment for acquired aplastic anemia in adults

Koster E, Halkes C, Bogers E, Hazenberg C, Heubel-Moenen F, Langemeier S, Meijer E, Nur E, Raaijmakers M, Snijders T, de Witte M, Tjon J, de Wreede L.

Background: Acquired aplastic anemia (AA) is characterized by an aplastic bone marrow and pancytopenia. Adult patients with AA can be treated with immunosuppressive treatment (IST) consisting of ATGAM in combination with cyclosporin (CsA) or with an allogeneic hematopoietic stem cell transplantation (alloSCT). Patients <40 years with an HLA-identical sibling preferentially receive an alloSCT. Other patients are treated with IST as 1st line treatment. IST leads to transfusion independency in the majority of patients but it can take up to 6 months before this response occurs. Some patients need long-term treatment with CsA to maintain this response and durable efficacy is hampered by relapsing aplasia or the development of MDS, AML or PNH. While graft versus host disease and relapse-free survival (GRFS) is used as a favorable composite outcome after alloSCT, a widely accepted measurement for treatment success after IST is missing.

Aims: In this study we examined Transplant, Treatment and Transfusion-free survival (TTT-free survival) as a relevant clinical outcome after standard IST with ATGAM and CsA in AA adult patients. We determined the 5-year TTT-free survival after standard IST in patients ≤40 years and >40 years.
Methods: The Dutch Adult Aplastic Anemia Registry started in 2014 and contains detailed data of all consecutive AA patients who have been treated with ATGAM-based therapy in the participating hospitals, offering a unique possibility to evaluate real-life long-term efficacy and safety of 1st line IST treatment in AA. To determine TTT-free survival, a multistate model (MSM) was developed, to take into account that patients can have transient periods of treatment success and failure. Patients started in the dynamic state treatment & transfusion at time of the start of ATGAM. This state also included all other (2nd line) non-alloSCT treatments (for example Eltrombopag, Rabbit-ATG or Danazol). Other dynamic states patients could enter and leave during follow-up were treatment & no transfusion, transfusion & no treatment and no treatment & no transfusion (considered as TTT-free survival). Absorbing states, accessible from all dynamic states, were death, alloSCT for AA, treatment for MDS/AML and treatment for PNH.
Results: ATGAM with CsA as 1st line treatment was started in 117 patients (median age 54 years, range 18-79). Overall survival after 5 year is 77% (95% Confidence Interval (95%CI) 67-86%) Figure Figure11 shows the results of the MSM. After 5 years, the TTT-free survival was 42% (95%CI: 33-55%) for the total cohort. 19% (95%CI: 12-31%) of the patients was transfusion independent but still needed medication at this time (mainly CsA or Eltrombopag). 15% (95%CI: 10-23%) had received an alloSCT as 2nd line treatment for AA, 5% (95%CI: 2-13%) had started treatment for MDS/AML and 2% (95%CI: 0-11%) had started treatment with complement inhibition for PNH. 5-year TTT-free survival was 60% (95%CI:44-82%) in patients aged ≤40 years (n=36), but only 33% (95%CI: 23-49%) in patients aged >40 years (n=81).
Summary/Conclusion: TTT-free survival can be used to evaluate treatment success after IST in AA patients, allowing achievement, loss and recovery of response. We showed that 5-year TTT-free survival is superior in patients ≤40 years compared to patients >40 years. This MSM can be used to predict outcomes in AA patients receiving IST and can help in the decision whether and when to offer a patient an alloSCT.

Gepubliceerd: Hemasphere. 2022;6(Suppl).
Impact factor: 8.300 ; Q1

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17. Impact of rituximab on treatment outcomes of patients with angioimmunoblastic T-cell lymphoma; a population-based analysis

Meeuwes FO, Brink M, van der Poel MWM, Kersten MJ, Wondergem M, Mutsaers P, Böhmer L, Woei AJS, Visser O, Oostvogels R, Jansen PM, Diepstra A, Snijders TJF, Plattel WJ, Huls GA, Vermaat JSP, Nijland M.

Background: Patients with angioimmunoblastic T-cell lymphoma (AITL) are treated with cyclophosphamide, doxorubicin, vincristine and prednisone with or without etoposide (CHO(E)P). In the majority of cases, Epstein-Barr virus (EBV)-positive B-cells are present in the tumour. There is paucity of research examining the effect of rituximab when added to CHO(E)P. In this nationwide, population-based study, we analysed the impact of rituximab on overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) of patients with AITL**.**
Methods: Patients with AITL diagnosed between 2014 and 2020 treated with ≥one cycle of CHO(E)P with or without rituximab were identified in the Netherlands Cancer Registry. Survival follow-up was up to 1st February 2022. Baseline characteristics, best response during first-line treatment and survival were collected. PFS was defined as the time from diagnosis to relapse or to all-cause-death. OS was defined as the time from diagnosis to all-cause-death. Multivariable analysis for the risk of mortality was performed using Cox regression**.**

Findings: Out of 335 patients, 146 patients (44%) received R-CHO(E)P. Rituximab was more frequently used in patients with a B-cell infiltrate (71% versus 89%, p < 0·01). The proportion of patients who received autologous stem cell transplantation (ASCT) was similar between CHO(E)P and R-CHO(E)P (27% versus 30%, respectively). The ORR and 2-year PFS for patients who received CHO(E)P and R-CHO(E)P were 71% and 78% (p = 0·01), and 40% and 45% (p = 0·12), respectively. The 5-year OS was 47% and 40% (p = 0·99), respectively. In multivariable analysis, IPI-score 3-5, no B-cell infiltrate and no ASCT were independent prognostic factors for risk of mortality, whereas the use of rituximab was not.
Interpretation: Although the addition of rituximab to CHO(E)P improved ORR for patients with AITL, the PFS and OS did not improve.

Gepubliceerd: Eur J Cancer. 2022;176:100-9.
Impact factor: 10.002 ; Q1

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18. Limiting systemic endocrine overtreatment in postmenopausal breast cancer patients with an ultralow classification of the 70-gene signature
Opdam M, van der Noort V, Kleijn M, Glas A, Mandjes I, Kleiterp S, Hilbers FS, Kruger DT, Bins AD, de Jong PC, Schiphorst P, van Dalen T, Flameling B, Rietbroek RC, Beeker A, van den Heiligenberg SM, Bakker SD, Wymenga ANM, Oving IM, Bijlsma RM, van Diest PJ, Vermorken JB, van Tinteren H, Linn SC.

Purpose: Guidelines recommend endocrine treatment for estrogen receptor-positive (ER+) breast cancers for up to 10 years. Earlier data suggest that the 70-gene signature (MammaPrint) has potential to select patients that have an excellent survival without chemotherapy and limited or no tamoxifen treatment. The aim was to validate the 70-gene signature ultralow-risk classification for endocrine therapy decision making**.**
Methods: In the IKA trial, postmenopausal patients with non-metastatic breast cancer had been randomized between no or limited adjuvant tamoxifen treatment without receiving chemotherapy. For this secondary analysis, FFPE tumor material was obtained of ER+HER2- patients with 0-3 positive lymph nodes and tested for the 70-gene signature. Distant recurrence-free interval (DRFI) long-term follow-up data were collected. Kaplan-Meier curves were used to estimate DRFI, stratified by lymph node status, for the three predefined 70-gene signature risk groups**.**
Results: A reliable 70-gene signature could be obtained for 135 patients. Of the node-negative and node-positive patients, respectively, 20% and 13% had an ultralow-risk classification. No DRFI events were observed for node-negative patients with an ultralow-risk score in the first 10 years. The 10-year DRFI was 90% and 66% in the low-risk (but not ultralow) and high-risk classified node-negative patients, respectively**.**
Conclusion: These survival analyses indicate that the postmenopausal node-negative ER+HER2- patients with an ultralow-risk 70-gene signature score have an excellent 10-year DRFI after surgery with a median of 1 year of endocrine treatment. This is in line with published results of the STO-3 randomized clinical trial and supports the concept that it is possible to reduce the duration of endocrine treatment in selected patients.

Gepubliceerd: Breast Cancer Res Treat. 2022;194(2):265-78.
Impact factor: 4.624; Q2

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19. Systemic Therapy in Advanced Nodular Melanoma versus Superficial Spreading Melanoma: A Nation-Wide Study of the Dutch Melanoma Treatment Registry

Rauwerdink DJW, van Doorn R, van der Hage J, Van den Eertwegh AJM, Haanen J, Aarts M, Berkmortel F, Blank CU, Boers-Sonderen MJ, De Groot JWB, Hospers GAP, de Meza M, Piersma D, Van Rijn RS, Stevense M, Van der Veldt A, Vreugdenhil G, Wouters M, Suijkerbuijk K, van der Kooij M, Kapiteijn E.

Nodular melanoma (NM) is associated with a higher locoregional and distant recurrence rate compared with superficial spreading melanoma (SSM); it is unknown whether the efficacy of systemic therapy is limited. Here, we compare the efficacy of immunotherapy and BRAF/MEK inhibitors (BRAF/MEKi) in advanced NM to SSM. Patients with advanced stage IIIc and stage IV NM and SSM treated with anti-CTLA-4 and/or anti-PD-1, or BRAF/MEKi in the first line, were included from the prospective Dutch Melanoma Treatment Registry. The primary objectives were distant metastasis-free survival (DMFS) and overall survival (OS). In total, 1086 NM and 2246 SSM patients were included. DMFS was significantly shorter for advanced NM patients at 1.9 years (CI 95% 0.7-4.2) compared with SSM patients at 3.1 years (CI 95% 1.3-6.2) (p < 0.01). Multivariate survival analysis for immunotherapy and BRAF/MEKi demonstrated a hazard ratio for immunotherapy of 1.0 (CI 95% 0.85-1.17) and BRAF/MEKi of 0.95 (CI 95% 0.81-1.11). A shorter DMFS for NM patients developing advanced disease compared with SSM patients was observed, while no difference was observed in the efficacy of systemic immunotherapy or BRAF/MEKi between NM and SSM patients. Our results suggests that the worse overall survival of NM is mainly driven by propensity of metastatic outgrowth of NM after primary diagnosis.

Gepubliceerd: Cancers (Basel). 2022;14(22).
Impact factor: 6.575; Q1

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20. Respiratory support in patients with severe COVID-19 in the International Severe Acute Respiratory and Emerging Infection (ISARIC) COVID-19 study: a prospective, multinational, observational study
Reyes LF, Murthy S, Garcia-Gallo E, Merson L, Ibáñez-Prada ED, Rello J, Fuentes YV, Martin-Loeches I, Bozza F, Duque S, Taccone FS, Fowler RA, Kartsonaki C, Gonçalves BP, Citarella BW, Aryal D, Burhan E, Cummings MJ, Delmas C, Diaz R, Figueiredo-Mello C, Hashmi M, Panda PK, Jiménez MP, Rincon DFB, Thomson D, Nichol A, Marshall JC, Olliaro PL, ISARIC Characterization Group: Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H..

Background: Up to 30% of hospitalised patients with COVID-19 require advanced respiratory support, including high-flow nasal cannulas (HFNC), non-invasive mechanical ventilation (NIV), or invasive mechanical ventilation (IMV). We aimed to describe the clinical characteristics, outcomes and risk factors for failing non-invasive respiratory support in patients treated with severe COVID-19 during the first two years of the pandemic in high-income countries (HICs) and low middle-income countries (LMICs)**.**
Methods: This is a multinational, multicentre, prospective cohort study embedded in the ISARIC-WHO COVID-19 Clinical Characterisation Protocol. Patients with laboratory-confirmed SARS-CoV-2 infection who required hospital admission were recruited prospectively. Patients treated with HFNC, NIV, or IMV within the first 24 h of hospital admission were included in this study. Descriptive statistics, random forest, and logistic regression analyses were used to describe clinical characteristics and compare clinical outcomes among patients treated with the different types of advanced respiratory support**.**
Results: A total of 66,565 patients were included in this study. Overall, 82.6% of patients were treated in HIC, and 40.6% were admitted to the hospital during the first pandemic wave. During the first 24 h after hospital admission, patients in HICs were more frequently treated with HFNC (48.0%), followed by NIV (38.6%) and IMV (13.4%). In contrast, patients admitted in lower- and middle-

income countries (LMICs) were less frequently treated with HFNC (16.1%) and the majority received IMV (59.1%). The failure rate of non-invasive respiratory support (i.e. HFNC or NIV) was 15.5%, of which 71.2% were from HIC and 28.8% from LMIC. The variables most strongly associated with non-invasive ventilation failure, defined as progression to IMV, were high leukocyte counts at hospital admission (OR [95%CI]; 5.86 [4.83-7.10]), treatment in an LMIC (OR [95%CI]; 2.04 [1.97-2.11]), and tachypnoea at hospital admission (OR [95%CI]; 1.16 [1.14-1.18]). Patients who failed HFNC/NIV had a higher 28-day fatality ratio (OR [95%CI]; 1.27 [1.25-1.30]).
Conclusions: In the present international cohort, the most frequently used advanced respiratory support was the HFNC. However, IMV was used more often in LMIC. Higher leucocyte count, tachypnoea, and treatment in LMIC were risk factors for HFNC/NIV failure. HFNC/NIV failure was related to worse clinical outcomes, such as 28-day mortality. Trial registration This is a prospective observational study; therefore, no health care interventions were applied to participants, and trial registration is not applicable.

Gepubliceerd: Crit Care. 2022;26(1):276.
Impact factor: 19.344; Q1

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21. Clofarabine added to intensive treatment in adult patients with newly diagnosed ALL: the HOVON-100 trial
Rijneveld AW, van der Holt B, de Weerdt O, Biemond BJ, van de Loosdrecht AA, van der Wagen LE, Bellido M, van Gelder M, van der Velden W, Selleslag D, van Lammeren-Venema D, Halkes CJM, Fijnheer R, Havelange V, van Sluis GL, Legdeur MC, Deeren D, Gadisseur A, Sinnige HAM, Breems DA, Jaspers A, Legrand O, Terpstra WE, Boersma RS, Mazure D, Triffet A, Tick LW, Beel K, Maertens JA, Beverloo HB, Bakkus M, Homburg CHE, de Haas V, van der Velden VHJ, Cornelissen JJ.

Clofarabine (CLO) is a nucleoside analog with efficacy in relapsed/refractory acute lymphoblastic leukemia (ALL). This randomized phase 3 study aimed to evaluate whether CLO added to induction and whether consolidation would improve outcome in adults with newly diagnosed ALL. Treatment of younger (18-40 years) patients consisted of a pediatric-inspired protocol, and for older patients (41-70 years), a semi-intensive protocol was used. Three hundred and forty patients were randomized. After a median follow-up of 70 months, 5-year event-free survival (EFS) was 50% and 53% for arm A and B (CLO arm). For patients ≤40 years, EFS was 58% vs 65% in arm A vs B, whereas in patients >40 years, EFS was 43% in both arms. Complete remission (CR) rate was 89% in both arms and similar in younger and older patients. Minimal residual disease (MRD) was assessed in 200 patients (60%). Fifty-four of 76 evaluable patients (71%) were MRD- after consolidation 1 in arm A vs 75/81 (93%) in arm B (P = .001). Seventy (42%) patients proceeded to allogeneic hematopoietic stem cell transplantation in both arms. Five-year overall survival (OS) was similar in both arms: 60% vs 61%. Among patients achieving CR, relapse rates were 28% and 24%, and nonrelapse mortality was 16% vs 17% after CR. CLO-treated patients experienced more serious adverse events, more infections, and more often went off protocol. This was most pronounced in older patients. We conclude that, despite a higher rate of MRD negativity, addition of CLO does not improve outcome in adults with ALL, which might be due to increased toxicity. This trial was registered at www.trialregister.nl as #NTR2004.

Gepubliceerd: Blood Adv. 2022;6(4):1115-25.
Impact factor: 7.642 ; Q1

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22. Tumor-Infiltrating Lymphocyte Therapy or Ipilimumab in Advanced Melanoma

Rohaan MW, Borch TH, van den Berg JH, Met Ö, Kessels R, Geukes Foppen MH, Stoltenborg Granhøj J, Nuijen B, Nijenhuis C, Jedema I, van Zon M, Scheij S, Beijnen JH, Hansen M, Voermans C, Noringriis IM, Monberg TJ, Holmstroem RB, Wever LDV, van Dijk M, Grijpink-Ongering LG, Valkenet LHM, Torres Acosta A, Karger M, Borgers JSW, Ten Ham RMT, Retèl VP, van Harten WH, Lalezari F, van Tinteren H, van der Veldt AAM, Hospers GAP, Stevense-den Boer MAM, Suijkerbuijk KPM, Aarts MJB, Piersma D, van den Eertwegh AJM, de Groot JB, Vreugdenhil G, Kapiteijn E, Boers-Sonderen MJ, Fiets WE, van den Berkmortel F, Ellebaek E, Hölmich LR, van Akkooi ACJ, van Houdt WJ, Wouters M, van Thienen JV, Blank CU, Meerveld-Eggink A, Klobuch S, Wilgenhof S, Schumacher TN, Donia M, Svane IM, Haanen J.

Background: Immune checkpoint inhibitors and targeted therapies have dramatically improved outcomes in patients with advanced melanoma, but approximately half these patients will not have a durable benefit. Phase 1-2 trials of adoptive cell therapy with tumor-infiltrating lymphocytes (TILs) have shown promising responses, but data from phase 3 trials are lacking to determine the role of TILs in treating advanced melanoma**.**
Methods: In this phase 3, multicenter, open-label trial, we randomly assigned patients with unresectable stage IIIC or IV melanoma in a 1:1 ratio to receive TIL or anti-cytotoxic T-lymphocyte antigen 4 therapy (ipilimumab at 3 mg per kilogram of body weight). Infusion of at least 5×10(9) TILs was preceded by nonmyeloablative, lymphodepleting chemotherapy (cyclophosphamide plus fludarabine) and followed by high-dose interleukin-2. The primary end point was progression-free survival**.**
Results: A total of 168 patients (86% with disease refractory to anti-programmed death 1 treatment) were assigned to receive TILs (84 patients) or ipilimumab (84 patients). In the intention-to-treat population, median progression-free survival was 7.2 months (95% confidence interval [CI], 4.2 to 13.1) in the TIL group and 3.1 months (95% CI, 3.0 to 4.3) in the ipilimumab group (hazard ratio for progression or death, 0.50; 95% CI, 0.35 to 0.72; P<0.001); 49% (95% CI, 38 to 60) and 21% (95% CI, 13 to 32) of the patients, respectively, had an objective response. Median overall survival was 25.8 months (95% CI, 18.2 to not reached) in the TIL group and 18.9 months (95% CI, 13.8 to 32.6) in the ipilimumab group. Treatment-related adverse events of grade 3 or higher occurred in all patients who received TILs and in 57% of those who received ipilimumab; in the TIL group, these events were mainly chemotherapy-related myelosuppression.
Conclusions: In patients with advanced melanoma, progression-free survival was significantly longer among those who received TIL therapy than among those who received ipilimumab. (Funded by the Dutch Cancer Society and others; ClinicalTrials.gov number, NCT02278887.).

Gepubliceerd: N Engl J Med. 2022;387(23):2113-25.
Impact factor: 176.082 ; Q1

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23. Timely administration of tocilizumab improves outcome of hospitalized COVID-19 patients
Rutgers A, Westerweel PE, van der Holt B, Postma S, van Vonderen MGA, Piersma DP, Postma D, van den Berge M, Jong E, de Vries M, van der Burg L, Huugen D, van der Poel M, Kampschreur LM, Nijland M, Strijbos JH, Tamminga M, Mutsaers P, Schol-Gelok S, Dijkstra-Tiekstra M, Sidorenkov G, Vincenten J, van Geffen WH, Knoester M, Kosterink J, Gans R, Stegeman C, Huls G, van Meerten T.

Introduction: The aim of this study was to determine the efficacy of early tocilizumab treatment for hospitalized patients with COVID-19 disease**.**
Methods: Open-label randomized phase II clinical trial investigating tocilizumab in patients with proven COVID-19 admitted to the general ward and in need of supplemental oxygen. The primary endpoint of the study was 30-day mortality with a prespecified 2-sided significance level of $\alpha = 0.10$. A post-hoc analysis was performed for a combined endpoint of mechanical ventilation or death at 30

days. Secondary objectives included comparing the duration of hospital stay, ICU admittance and duration of ICU stay and the duration of mechanical ventilation**.**
Results: A total of 354 patients (67% men; median age 66 years) were enrolled of whom 88% received dexamethasone. Thirty-day mortality was 19% (95% CI 14%-26%) in the standard arm versus 12% (95% CI: 8%-18%) in the tocilizumab arm, hazard ratio (HR) = 0.62 (90% CI 0.39-0.98; p = 0.086). 17% of patients were admitted to the ICU in each arm (p = 0.89). The median stay in the ICU was 14 days (IQR 9-28) in the standard arm versus 9 days (IQR 5-14) in the tocilizumab arm (p = 0.014). Mechanical ventilation or death at thirty days was 31% (95% CI 24%-38%) in the standard arm versus 21% (95% CI 16%-28%) in the tocilizumab arm, HR = 0.65 (95% CI 0.42-0.98; p = 0.042).
Conclusions: This randomized phase II study supports efficacy for tocilizumab when given early in the disease course in hospitalized patients who need oxygen support, especially when concomitantly treated with dexamethasone.
Trial registration: https://www.trialregister.nl/trial/8504.

Gepubliceerd: PLoS One. 2022;17(8):e0271807.
Impact factor: 3.752 ; Q2

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24. Physical Activity Is Associated with Improved Overall Survival among Patients with Metastatic Colorectal Cancer
Smit KC, Derksen JWG, Beets GLO, Belt EJT, Berbée M, Coene P, van Cruijsen H, Davidis MA, Dekker JWT, van Dodewaard-de Jong JM, Haringhuizen AW, Helgason HH, Hendriks MP, Hoekstra R, de Hingh I, JNM IJ, Janssen JJB, Konsten JLM, Los M, Mekenkamp LJM, Nieboer P, Peeters K, Peters N, Pruijt H, Quarles van Ufford-Mannesse P, Rietbroek RC, Schiphorst AHW, Schouten van der Velden A, Schrauwen RWM, Sie MPS, Sommeijer DW, Sonneveld DJA, Stockmann H, Tent M, Terheggen F, Tjin ATMLR, Valkenburg-van Iersel L, van der Velden AMT, Vles WJ, van Voorthuizen T, Wegdam JA, de Wilt JHW, Koopman M, May AM, On Behalf Of The Plcrc Study G.

Regular physical activity (PA) is associated with improved overall survival (OS) in stage I-III colorectal cancer (CRC) patients. This association is less defined in patients with metastatic CRC (mCRC). We therefore conducted a study in mCRC patients participating in the Prospective Dutch Colorectal Cancer cohort. PA was assessed with the validated SQUASH questionnaire, filled-in within a maximum of 60 days after diagnosis of mCRC. PA was quantified by calculating Metabolic Equivalent Task (MET) hours per week. American College of Sports and Medicine (ACSM) PA guideline adherence, tertiles of moderate to vigorous PA (MVPA), and sport and leisure time MVPA (MVPA-SL) were assessed as well. Vital status was obtained from the municipal population registry. Cox proportional-hazards models were used to study the association between PA determinants and all-cause mortality adjusted for prognostic patient and treatment-related factors. In total, 293 mCRC patients (mean age 62.9 ± 10.6 years, 67% male) were included in the analysis. Compared to low levels, moderate and high levels of MET-hours were significantly associated with longer OS (fully adjusted hazard ratios: 0.491, (95% CI 0.299-0.807, p value = 0.005) and 0.485 (95% CI 0.303-0.778, p value = 0.003), respectively), as were high levels of MVPA (0.476 (95% CI 0.278-0.816, p value = 0.007)) and MVPA-SL (0.389 (95% CI 0.224-0.677, p value < 0.001)), and adherence to ACSM PA guidelines compared to non-adherence (0.629 (95% CI 0.412-0.961, p value = 0.032)). The present study provides evidence that higher PA levels at diagnosis of mCRC are associated with longer OS.

Gepubliceerd: Cancers (Basel). 2022;14(4).
Impact factor: 6.575; Q1

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25. Survival of stage IV melanoma in Belgium and the Netherlands

Suijkerbuijk KPM, Haanen J, Boers-Sonderen MJ, Hospers GAP, Blank CU, van den Berkmortel F, de Groot JWB, Piersma D, Aarts MJB, van Rijn RS, Vreugdenhil G, Westgeest HM, Kapiteijn E, van der Veldt AAM, van den Eertwegh AJM.

Gepubliceerd: J Eur Acad Dermatol Venereol. 2022;36(2):e118-e9.
Impact factor: 9.228 ; Q1

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26. Delayed Diagnosis of Severe Hypoglycemia in a Septic Patient With Chronic Renal Failure
Ten Berge D, Manning F, Silderhuis V, Deijns S, Pouwels MJ, Krabbe H, Beishuizen A.

High-dose vitamin C therapy has gained increased interest as an adjunctive treatment of septic shock, although convincing evidence is still lacking. High blood levels of vitamin C may interfere with several point-of-care blood glucose meters. We describe the case of a 67-year-old septic patient known with chronic renal failure who developed truly severe hypoglycemia, which was masked by spuriously high glucose values measured on a capillary blood glucose meter. This initially led to the treatment of spurious hyperglycemia with high-dose insulin and a delayed correct diagnosis and treatment, rendering substantial risk for the patient. Awareness of this dangerous interference is warranted.

Gepubliceerd: Cureus. 2022;14(8):e28615.
Impact factor: 0 ; Q NVT

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27. End-of-Life Use of Systemic Therapy in Patients With Advanced Melanoma: A Nationwide Cohort Study
van Breeschoten J, Ismail RK, Wouters M, Hilarius DL, de Wreede LC, Haanen JB, Blank CU, Aarts MJB, van den Berkmortel F, de Groot JWB, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Stevense-den Boer MA, van der Veldt AAM, Vreugdenhil G, Boers-Sonderen MJ, Suijkerbuijk KPM, van den Eertwegh AJM.

Purpose: The introduction of immune checkpoint inhibitors and targeted therapies improved the overall survival of patients with advanced melanoma. It is not known how often these costly treatments with potential serious side effects are ineffectively applied in the last phase of life. This study aimed to investigate the start of a new systemic therapy within 45 and 90 days of death in Dutch patients with advanced melanoma**.**
Methods: We selected patients who were diagnosed with unresectable IIIC or stage IV melanoma, registered in the Dutch Melanoma Treatment Registry, and died between 2013 and 2019. Primary outcome was the probability of starting a new systemic therapy 45 and 90 days before death. Secondary outcomes were type of systemic therapy started, grade 3/4 adverse events (AEs), and the total costs of systemic therapies**.**
Results: Between 2013 and 2019, 3,797 patients with unresectable IIIC or stage IV melanoma were entered in the registry and died. The percentage of patients receiving a new systemic therapy within 45 and 90 days before death was significantly different between Dutch melanoma centers (varying from 6% to 23% and 20% to 46%, respectively). Thirteen percent of patients (n = 146) developed grade 3/4 AEs in the last period before death. The majority of patients with an AE required hospital admission (n = 102, 69.6%). Mean total costs of systemic therapy per cohort year of the patients who received a new systemic therapy within 90 days before death were 2.3%-2.8% of the total costs spent on melanoma therapies**.**

Conclusion: The minority of Dutch patients with metastatic melanoma started a new systemic therapy in the last phase of life. However, the percentages varied between Dutch melanoma centers. Financial impact of these therapies in the last phase of life is relatively small.

Gepubliceerd: JCO Oncol Pract. 2022;18(10):e1611-e20.
Impact factor: 3.487 ; Q3

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28. Correction: First-line BRAF/MEK inhibitors versus anti-PD-1 monotherapy in BRAF(V600)-mutant advanced melanoma patients: a propensity-matched survival analysis
van Breeschoten J, Wouters M, Hilarius DL, Haanen JB, Blank CU, Aarts MJB, van den Berkmortel F, de Groot JB, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Suijkerbuijk KPM, Blokx WAM, Tije BJT, Veldt A, Vreugdenhil A, Boers-Sonderen MJ, van den Eertwegh AJM.

Gepubliceerd: Br J Cancer. 2022;126(9):1362.
Impact factor: 9.082; Q1

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29. Serum cytokine levels are associated with tumor progression during FOLFIRINOX chemotherapy and overall survival in pancreatic cancer patients
van der Sijde F, Dik WA, Mustafa DAM, Vietsch EE, Besselink MG, Debets R, Koerkamp BG, Haberkorn BCM, Homs MYV, Janssen QP, Luelmo SAC, Mekenkamp LJM, Oostvogels AAM, Smits-Te Nijenhuis MAW, Wilmink JW, van Eijck CHJ.

Background: Biomarkers predicting treatment response may be used to stratify patients with pancreatic ductal adenocarcinoma (PDAC) for available therapies. The aim of this study was to evaluate the association of circulating cytokines with FOLFIRINOX response and with overall survival (OS)**.**
Methods: Serum samples were collected before start and after the first cycle of FOLFIRINOX from patients with PDAC (n=83) of all disease stages. Overall, 34 circulating cytokines were analyzed with a multiplex immunoassay. In addition, changes in peripheral blood immune cell counts were determined by flow cytometry to correlate with differences in cytokine levels. Chemotherapy response was determined by CT scans with the RECIST 1.1 criteria, as disease control (n=64) or progressive disease (n=19) within eight cycles of FOLFIRINOX**.**
Results: Patients with high serum IL-1RA concentrations after one cycle of chemotherapy were less likely to have tumor progression during FOLFIRINOX (OR 0.25, P=0.040). Increase of circulating IL-1RA concentrations correlated with increase of total, classical (CD14+CD16-), and non-classical monocytes (CD14-CD16+), and dendritic cells. In multivariable cox regression, including the variables chemotherapy response outcome and baseline CA19-9 level, serum concentrations of IL-7 (HR 2.14, P=0.010), IL-18 (HR 2.00, P=0.020), and MIP-1β (HR 0.51, P=0.025) after one cycle of FOLFIRINOX showed correlations with OS.
Conclusions: Circulating IL-1RA, IL-7, IL-18, and MIP-1β concentrations are biomarkers associated with FOLFIRINOX response in PDAC patients, suggesting an important role for specific immune cells in chemotherapy response and PDAC progression. Cytokine-based treatment might improve patient outcome and should be evaluated in future studies.

Gepubliceerd: Front Immunol. 2022;13:898498.
Impact factor: 8.787 ; Q1

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30. Differences in hospitalisation between peritoneal dialysis and haemodialysis patients

van Eck van der Sluijs A, Bonenkamp AA, van Wallene VA, Hoekstra T, Lissenberg-Witte BI, Dekker FW, van Ittersum FJ, Verhaar MC, van Jaarsveld BC, Abrahams AC, HS DsgB.

Background: Dialysis is associated with frequent hospitalisations. Studies comparing hospitalisations between peritoneal dialysis (PD) and haemodialysis (HD) report conflicting results and mostly analyse data of patients that remain on their initial dialysis modality. This cohort study compares hospitalisations between PD and HD patients taking into account transitions between modalities**.**
Methods: The Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes collected hospitalisation data of patients who started dialysis between 2012 and 2017. Primary outcome was hospitalisation rate, analysed with a multi-state model that attributed each hospitalisation to the current dialysis modality**.**
Results: In total, 695 patients (252 PD, 443 HD) treated in 31 Dutch hospitals were included. The crude hospitalisation rate for PD was 2.3 (± 5.0) and for HD 1.4 (± 3.2) hospitalisations per patient-year. The adjusted hazard ratio for hospitalisation rate was 1.1 (95%CI 1.02-1.3) for PD compared with HD. The risk for first hospitalisation was 1.3 times (95%CI 1.1-1.6) higher for PD compared with HD during the first year after dialysis initiation. The number of hospitalisations and number of hospital days per patient-year were significantly higher for PD. The most common causes of PD and HD hospitalisations were peritonitis (23%) and vascular access-related problems (33%)**.**
Conclusion: PD was associated with higher hospitalisation rate, higher risk for first hospitalisation and higher number of hospitalisations compared with HD. Since the PD hospitalisations were mainly caused by peritonitis, more attention to infection prevention is necessary for reducing the number of hospitalisations in the future.

Gepubliceerd: Eur J Clin Invest. 2022;52(6):e13758.
Impact factor: IF 5.722 ; Q1

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31. BRAF and NRAS Mutation Status and Response to Checkpoint Inhibition in Advanced Melanoma

van Not OJ, Blokx WAM, van den Eertwegh AJM, de Meza MM, Haanen JB, Blank CU, Aarts MJB, van den Berkmortel F, de Groot JWB, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Stevense-den Boer M, van der Veldt AAM, Boers-Sonderen MJ, Jansen AML, Wouters M, Suijkerbuijk KPM.

Purpose: Little is known about the effect of specific gene mutations on efficacy of immune checkpoint inhibitors in patients with advanced melanoma.
Material and Methods: All patients with advanced melanoma treated with first-line anti-PD-1 or ipilimumab-nivolumab between 2012 and 2021 in the nationwide Dutch Melanoma Treatment Registry were included in this cohort study. Objective response rate, progression-free survival (PFS), and overall survival (OS) were analyzed according to BRAF and NRAS status. A multivariable Cox model was used to analyze prognostic factors associated with PFS and OS**.**
Results: In total, 1764 patients received anti-PD-1 and 759 received ipilimumab-nivolumab. No significant differences in PFS were found in the anti-PD-1 cohort. In the ipilimumab-nivolumab cohort, median PFS was significantly higher for BRAF-mutant melanoma (9.9 months; 95% CI, 6.8 to 17.2) compared with NRAS-mutant (4.8 months; 95% CI, 3.0 to 7.5) and double wild-type (5.3 months; 95% CI, 3.6 to 7.1). In multivariable analysis, BRAF-mutant melanoma was significantly associated with a lower risk of progression or death in the ipilimumab-nivolumab cohort. Median OS was significantly higher for BRAF-mutant melanoma compared with NRAS-mutant and double wild-type melanoma for both immune checkpoint inhibitor regimens**.**
Conclusion: Ipilimumab-nivolumab-treated patients with BRAF-mutant melanoma display improved PFS and OS compared with patients with NRAS-mutant and double wild-type melanoma. BRAF

mutation status is a factor to consider while choosing between mono and dual checkpoint inhibition in advanced melanoma.

Gepubliceerd: JCO Precis Oncol. 2022;6:e2200018.
Impact factor: 5.479 ; Q2

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32. Response to immune checkpoint inhibitors in acral melanoma: A nationwide cohort study
van Not OJ, de Meza MM, van den Eertwegh AJM, Haanen JB, Blank CU, Aarts MJB, van den Berkmortel F, van Breeschoten J, de Groot JB, Hospers GAP, Ismail RK, Kapiteijn E, Piersma D, van Rijn RS, Stevense-den Boer MAM, van der Veldt AAM, Vreugdenhil G, Bonenkamp HJ, Boers-Sonderen MJ, Blokx WAM, Wouters M, Suijkerbuijk KPM.

Background: Recent reports suggest the limited efficacy of immune checkpoints inhibitors in advanced acral melanoma (AM). This study aims to investigate the clinical outcomes of immune checkpoint inhibitors in patients with stage III and IV AM and compare them to cutaneous melanoma (CM)**.**
Methods: We included patients with advanced AM and CM treated with first-line anti-programmed cell death (PD)-1 monotherapy or ipilimumab-nivolumab registered in the prospective nationwide Dutch Melanoma Treatment Registry. Objective response rates, progression-free survival (PFS) and overall survival (OS) were calculated. A Cox proportional hazard model was used to assess the prognostic factors with PFS and OS**.**
Results: In total, 2058 patients (88 AM and 1970 CM) with advanced melanoma were included. First-line objective response rates were 34% for AM versus 54% for CM in the advanced anti-PD-1 cohort and 33% for AM versus 53% for CM in the advanced ipilimumab-nivolumab cohort. The Median PFS was significantly shorter for anti-PD-1 treated AM patients (3.1 months; 95%CI: 2.8-5.6) than patients with CM (10.1 months; 95%CI: 8.5-12.2) ($P < 0.001$). In patients with advanced melanoma, AM was significantly associated with a higher risk of progression (HRadj 1.63; 95%CI: 1.26-2.11; $P < 0.001$) and death (HRadj 1.54; 95%CI: 1.15-2.06; $P = 0.004$) than CM.
Conclusions: This study shows lower effectiveness of anti-PD -1 monotherapy and ipilimumab-nivolumab in AM, with lower response rates, PFS and OS than CM. This group of patients should be prioritised in the development of alternative treatment strategies.

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Impact factor: 10.002 ; Q1

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33. The unfavorable effects of COVID-19 on Dutch advanced melanoma care
van Not OJ, van Breeschoten J, van den Eertwegh AJM, Hilarius DL, De Meza MM, Haanen JB, Blank CU, Aarts MJB, van den Berkmortel F, de Groot JWB, Hospers GAP, Ismail RK, Kapiteijn E, Piersma D, van Rijn RS, Stevense-den Boer MAM, van der Veldt AAM, Vreugdenhil G, Boers-Sonderen MJ, Blokx WAM, Suijkerbuijk KPM, Wouters M.

The COVID-19 pandemic had a severe impact on medical care. Our study aims to investigate the impact of COVID-19 on advanced melanoma care in the Netherlands. We selected patients diagnosed with irresectable stage IIIc and IV melanoma during the first and second COVID-19 wave and compared them with patients diagnosed within the same time frame in 2018 and 2019. Patients were divided into three geographical regions. We investigated baseline characteristics, time from diagnosis until start of systemic therapy and postponement of anti-PD-1 courses. During both waves, fewer patients were diagnosed compared to the control groups. During the first wave, time between diagnosis and start of treatment was significantly longer in the southern region compared to other

regions (33 vs 9 and 15 days, P-value <.05). Anti-PD-1 courses were postponed in 20.0% vs 3.0% of patients in the first wave compared to the control period. Significantly more patients had courses postponed in the south during the first wave compared to other regions (34.8% vs 11.5% vs 22.3%, P-value <.001). Significantly more patients diagnosed during the second wave had brain metastases and worse performance status compared to the control period. In conclusion, advanced melanoma care in the Netherlands was severely affected by the COVID-19 pandemic. In the south, the start of systemic treatment for advanced melanoma was more often delayed, and treatment courses were more frequently postponed. During the second wave, patients were diagnosed with poorer patient and tumor characteristics. Longer follow-up is needed to establish the impact on patient outcomes.

Gepubliceerd: Int J Cancer. 2022;150(5):816-24.
Impact factor: 7.316 ; Q1

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34. Association of Immune-Related Adverse Event Management With Survival in Patients With Advanced Melanoma

van Not OJ, Verheijden RJ, van den Eertwegh AJM, Haanen J, Aarts MJB, van den Berkmortel F, Blank CU, Boers-Sonderen MJ, de Groot JB, Hospers GAP, Kamphuis AM, Kapiteijn E, May AM, de Meza MM, Piersma D, van Rijn R, Stevense-den Boer MA, van der Veldt AAM, Vreugdenhil G, Blokx WAM, Wouters MJM, Suijkerbuijk KPM.

Importance: Management of checkpoint inhibitor-induced immune-related adverse events (irAEs) is primarily based on expert opinion. Recent studies have suggested detrimental effects of anti-tumor necrosis factor on checkpoint-inhibitor efficacy.
Objective: To determine the association of toxic effect management with progression-free survival (PFS), overall survival (OS), and melanoma-specific survival (MSS) in patients with advanced melanoma treated with first-line ipilimumab-nivolumab combination therapy.
Design, Setting and participants: This population-based, multicenter cohort study included patients with advanced melanoma experiencing grade 3 and higher irAEs after treatment with first-line ipilimumab and nivolumab between 2015 and 2021. Data were collected from the Dutch Melanoma Treatment Registry. Median follow-up was 23.6 months.
Main Outcomes and Measures: The PFS, OS, and MSS were analyzed according to toxic effect management regimen. Cox proportional hazard regression was used to assess factors associated with PFS and OS**.**
Results: Of 771 patients treated with ipilimumab and nivolumab, 350 patients (median [IQR] age, 60.0 [51.0-68.0] years; 206 [58.9%] male) were treated with immunosuppression for severe irAEs. Of these patients, 235 received steroids alone, and 115 received steroids with second-line immunosuppressants. Colitis and hepatitis were the most frequently reported types of toxic effects. Except for type of toxic effect, no statistically significant differences existed at baseline. Median PFS was statistically significantly longer for patients treated with steroids alone compared with patients treated with steroids plus second-line immunosuppressants (11.3 [95% CI, 9.6-19.6] months vs 5.4 [95% CI, 4.5-12.4] months; P = .01). Median OS was also statistically significantly longer for the group receiving steroids alone compared with those receiving steroids plus second-line immunosuppressants (46.1 months [95% CI, 39.0 months-not reached (NR)] vs 22.5 months [95% CI, 36.5 months-NR]; P = .04). Median MSS was also better in the group receiving steroids alone compared with the group receiving steroids plus second-line immunosuppressants (NR [95% CI, 46.1 months-NR] vs 28.8 months [95% CI, 20.5 months-NR]; P = .006). After adjustment for potential confounders, patients treated with steroids plus second-line immunosuppressants showed a trend toward a higher risk of progression (adjusted hazard ratio, 1.40 [95% CI, 1.00-1.97]; P = .05) and had a higher risk of death (adjusted hazard ratio, 1.54 [95% CI, 1.03-2.30]; P = .04) compared with those receiving steroids alone.

Conclusions and Relevance: In this cohort study, second-line immunosuppression for irAEs was associated with impaired PFS, OS, and MSS in patients with advanced melanoma treated with first-line ipilimumab and nivolumab. These findings stress the importance of assessing the effects of differential irAE management strategies, not only in patients with melanoma but also other tumor types.

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Impact factor: 33.012 ; Q1

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35. Discontinuation of anti-PD-1 monotherapy in advanced melanoma-Outcomes of daily clinical practice
van Zeijl MCT, van den Eertwegh AJM, Wouters M, de Wreede LC, Aarts MJB, van den Berkmortel F, de Groot JB, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, van der Hoeven JJM, Haanen J.

There is no consensus on the optimal treatment duration of anti-PD-1 for advanced melanoma. The aim of our study was to gain insight into the outcomes of anti-PD-1 discontinuation, the association of treatment duration with progression and anti-PD-1 re-treatment in relapsing patients. Analyses were performed on advanced melanoma patients in the Netherlands who discontinued first-line anti-PD-1 monotherapy in the absence of progressive disease (n = 324). Survival was estimated after anti-PD-1 discontinuation and with a Cox model the association of treatment duration with progression was assessed. At the time of anti-PD-1 discontinuation, 90 (28%) patients had a complete response (CR), 190 (59%) a partial response (PR) and 44 (14%) stable disease (SD). Median treatment duration for patients with CR, PR and SD was 11.2, 11.5 and 7.2 months, respectively. The 24-month progression-free survival and overall survival probabilities for patients with a CR, PR and SD were, respectively, 64% and 88%, 53% and 82%, 31% and 64%. Survival outcomes of patients with a PR and CR were similar when anti-PD-1 discontinuation was not due to adverse events. Having a PR at anti-PD-1 discontinuation and longer time to first response were associated with progression [hazard ratio (HR) = 1.81 (95% confidence interval, CI = 1.11-2.97) and HR = 1.10 (95% CI = 1.02-1.19; per month increase)]. In 17 of the 27 anti-PD-1 re-treated patients (63%), a response was observed. Advanced melanoma patients can have durable remissions after (elective) anti-PD-1 discontinuation.

Gepubliceerd: Int J Cancer. 2022;150(2):317-26.
Impact factor: 7.316 ; Q1

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36. Effects of HLA Mismatches on Cytokine Release Syndrome and Associated Non-Relapse Mortality in Allogeneic Stem Cell Transplantation with Post-Transplant Cyclophosphamide
Von Dem Borne PA, Kemps-Mols BM, de Wreede LC, van Beek AA, Snijders TJF, van Lammeren D, Tijmensen J, Sijs-Szabo A, Nering Bögel TL, Oudshoorn MA, Halkes CJM, van Balen P, Marijt EWAF, Tjon JML, Vermaat JSP, Veelken H.

Background: Post-transplant cyclophosphamide (PTCy) is an effective method for graft versus host disease prevention in allogeneic stem cell transplantation (alloSCT). The alloreactive T-cell response in the first days after PTCy-alloSCT can induce a systemic inflammatory response known as cytokine release syndrome (CRS). The incidence of CRS appears to increase with higher degrees of HLA mismatch between patient and donor. In haplo-identical PTCy-alloSCT, CRS occurs frequently (73-94%) and has a negative impact on non-relapse mortality (NRM) and survival. In 10/10 HLA matched related and unrelated allogeneic stem cell transplantation (MRD/MUD PTCy-alloSCT), CRS is less

frequently observed (14-23%) without effects on NRM and survival. The specific contributions of different HLA mismatches in CRS development are not well known.
Aim: To study the effects of HLA mismatching in MRD/MUD PTCy-alloSCT transplantation on development of CRS and CRS-associated NRM and survival.
Methods: We retrospectively studied CRS, survival and NRM in a group of 97 MRD/MUD PTCy-alloSCT patients with different degrees of HLA matching (20% of patients were 12/12, 50% 10/10 and 30% 9/10 HLA-matched).
Results: CRS developed in 69% of patients, mostly grade 1 (85%), 12% grade 2 and 3% grade 3. CRS developed significantly more in patients transplanted with a 9/10 or 10/10 match compared to a 12/12 match (90% and 75% versus 26%). By focusing on the maximum grade of fever developing during CRS, CRS severity grading was refined, revealing effects of specific HLA mismatches on CRS. In 10/10 matched patients, HLA-DPB1 non-permissiveness significantly increased grade 2-3 fever CRS incidence from 10 to 62%. Although regarded to be unimportant in HLA matching, single HLA-DRB3/4/5 mismatches could induce grade 3 fever CRS. Strongest effects on fever developed in 9/10 matched patients (35% grade 3 fever CRS), showing differences between various HLA mismatch groups. HLA-DRB1 mismatches induced significantly higher fever than HLA-C mismatches. The total number of HLA mismatches (combined HLA-A, B, C, DRB1, DRB3/4/5, DQ and DP non-permissive mismatches) was found to correlate with the height of fever developing. Importantly, patients with grade 3 fever CRS showed significantly increased NRM and significantly inferior survival compared to patients with grade 0-2 fever CRS.
Conclusions: In contrast to earlier publications in which CRS was demonstrated mainly in haplo-identical PTCy-alloSCT, we show that also in HLA matched related and unrelated PTCy-alloSCT incidence of CRS can be high and influence transplantation results. Development of CRS is dependent on the degree of HLA matching (90% in 9/10, 75% in 10/10 and 26% in 12/12 matched patients). By focusing on the maximum grade of fever developing during CRS, CRS severity grading can be refined, revealing effects of specific HLA mismatches on CRS. The height of fever during CRS is dependent on the number and types of HLA mismatches. CRS with grade 3 fever increases NRM and decreases survival. HLA matching decisions may be used to prevent grade 3 fever CRS, and thereby possibly also NRM. Alternatively, anti-inflammatory interventions may be considered in patients developing grade 3 fever early after alloSCT.

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Impact factor: 22.669 ; Q1

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37. Prophylactic Donor Lymphocyte Infusion in Patients after Allogeneic Stem Cell Transplantation with Post-Transplant Cyclophosphamide Is Associated with Low Relapse Risk and Excellent Survival in Patients below 65 Years with Acute Myeloid Leukemia and High-Risk Myelodysplasia
Von Dem Borne PA, Snijders TJF, van Lammeren D, Tijmensen J, Planken EV, Levenga H, van den Berg Y, Marijt EW, van Balen P, Tjon JM, Vermaat JSP, Nering Bögel TL, Oudshoorn MA, Halkes CJM, Veelken H.

Background: Post-transplant cyclophosphamide (PTCy) effectively prevents graft-versus-host-disease (GVHD) in allogeneic stem cell transplantation (alloSCT) with matched related and matched unrelated donors resulting in low risk of non-relapse mortality (NRM) (<10%). However, PTCy-alloSCT is associated with high relapse rates of approximately 20-30% after 1 year and 30-40% after 2 years (Gooptu et al. Blood 2021, Ruggeri et al. J Hemat Oncol 2018). Prophylactic donor lymphocyte infusion (DLI) may reduce relapse, although it may increase the risk of GVHD.
Aim: To provide evidence for reduction of relapse and improvement of survival by combining allogeneic SCT with PTCy and subsequent standardized prophylactic donor lymphocyte infusions (DLI) in a cohort of patients with acute myeloid leukemia (AML) and high risk myelodysplasia (MDS).

Patients and Methods: Sixty-five patients with AML (n=50) or high risk MDS (n=15) received myeloablative (n=15) or reduced-intensity (n=50) alloSCT with a matched related (n=8) or 9/10 (n=19) or 10/10 (n=38) matched unrelated donor. Based on modified ELN criteria, 10 AML patients were intermediate risk and 40 poor risk. GVHD prophylaxis consisted of PTCy, mycophenolate until day +30, and tacrolimus tapered from +70 (related or 10/10 unrelated) or day +90 (9/10 unrelated). All patients were planned to receive DLI at 6 months after transplantation at a dose of 3 x 10^6 CD3+ cells/kg in related and 1.5 x 10^6 CD3+ cells/kg in unrelated alloSCT. In poor risk patients (poor risk AML and high risk MDS) additional low dose DLI (0.3 or 0.15 x 10^6 CD3+ cells/kg in related and unrelated alloSCT, respectively) was planned one month after tacrolimus tapering (i.e. 3-4 months after alloSCT). In poor risk patients with a sensitive molecular or immunophenotypical minimal residual disease (MRD) marker (<0.1%) low dose DLI was not administered but MRD monitored; only in case of MRD positivity at 2 or 4 months additional low dose DLI was given.
Results: Of the 65 patients, 49 received standard dose DLI at 6 months after alloSCT (75%), either as a first dose at 6 months (40%), or as a second DLI after a low dose DLI at 3-4 months after alloSCT (35%). Reasons for not receiving standard dose DLI were NRM (5%), GVHD (9%), relapse (9%) and donor-related (2%).
Of the 22 poor risk patients with a sensitive MRD marker, 15 received the first DLI at 6 months; 6 received both low dose DLI and 6 month DLI because of MRD positivity at 2 or 4 months after alloSCT; one patient did not receive prophylactic DLI because of systemic relapse at day 105.
With a median follow up of 400 days (range 183-814), 12 patients developed systemic relapse. Most relapses (67%) occurred very early after transplant (median 110 days, range 63 to 165 days), before low dose DLI could be effectively given. These early relapses occurred significantly more in patients >= 65 years (88%) than <65 years (p=0.01 Fisher's exact).
Overall survival at 1 year was 95% (95% CI 89-100%) in patients <65 (n=42), significantly higher than the 68% (95% CI 49-95%) in patients >=65 (n=23) (p=0.01). Relapse rate at 1 year was 5% (95% CI 1-15%) in patients <65, significantly lower than the 37% (95% CI 25-58%) in patients >=65 (p=0.001). Grade 2-4 acute and chronic GVHD incidence at 1 year was low (6% (95% CI 2-14%) and 11% (2.5-25%), respectively).
Survival at 1 year was similar (p=0.35) in poor risk patients without MRD marker (80%, 95% CI 67-96%), poor risk with MRD marker (95%, 95% CI 87-100%) and intermediate risk (86%, 95% CI 63-100%). For these groups relapse risk was also similar: 18% (95% CI 7-33%), 16% (95% CI 3-36%) and 11% (95% CI 5-41%), respectively.
Conclusions: This study is the first to demonstrate feasibility of prophylactic DLI after PTCy-alloSCT with a low associated risk of GVHD. The observed low incidence of relapse at 1 year after transplantation (5%) of patients aged <65 years appears to be substantially less than the reported risk without pre-planned DLI (20-30%). Although the value of early DLI administration (around 3-4 months) is still unclear, standard dose DLI administration at 6 months appears feasible in intermediate risk patients and poor risk patients with sensitive MRD markers. Early relapses after alloSCT, at a time point before early DLI could be effective, caused the inferior survival of patients aged >= 65 years. The results of this study can serve as a reference for designing future prophylactic cellular interventions in the PTCy-alloSCT setting.

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Impact factor: 22.669 ; Q1

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38. Plasma Extracellular Vesicle-Associated microRNAs for Early Response Prediction in Patients with High-Grade B-Cell Lymphoma

Wang S, Drees EEE, Gómez-Martín C, De Jonge A, van Eijndhoven M, Groenewegen N, Veldt-Verkuijlen S, Nijland M, Van Der Poel MWM, Sandberg Y, van Rijn R, Mutsaers P, Vergote VKJ, Kersten

MJ, Bilgin YM, Stevens WBC, Durian M, Snijders TJF, de Jong D, Zijlstra JM, Chamuleau MED, Pegtel DM.

Background: Early and accurate outcome prediction is essential in the clinical management of high-grade B-cell lymphoma (HGBL). An early switch to salvage treatments for those patients who are likely to develop refractory/relapsed disease may improve overall survival. Unfortunately, the positive predictive value of an interim PET-CT is not high enough to guide treatment decisions. Extracellular vesicle-associated microRNAs (EV-miRNAs) are considered promising liquid biopsy-based biomarkers for lymphomas. We performed small RNA sequencing of plasma samples collected during treatment and applied machine learning to build EV-miRNA signatures for early response prediction in patients with HGBL with MYC and BCL2 and/or BCL6 rearrangements (HGBL-DH/TH).
Methods: We analyzed PAXgene ccfDNA plasma samples, from 38 of the 97 patients included in the HOVON-152 trial (NCT03620578), a prospective, multicenter, non-randomized phase II trial. In this trial, patients with HGBL-DH/TH receive one cycle of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) followed by five cycles of dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R). Patients who achieve complete metabolic response (CMR) at the end-of-induction (EOI) receive one year of nivolumab consolidation. Response was assessed by an EOI PET-CT and classified as CMR (Deauville score 1-3) (responders) or no-CMR (non-responders). 20 responders and 18 non-responders (enrichment for non-responders), were selected for this analysis. We isolated plasma EVs with size exclusion chromatography as confirmed with transmission electron microscopy (TEM), tunable resistive pulse sensing (TRPS), and western blot (WB). Library preparation was done according to an unbiased, unique molecular identifier (UMI)-enhanced small RNA sequencing protocol (IsoSeek) (van Eijndhoven et al., 2021. bioRxiv) and sequenced on the NovaSeq 6000 (Illumina). We applied machine learning including the least absolute shrinkage and selection operator (LASSO), Elastic Net, and Ridge Regression to build models with EV-miRNAs for early EOI response prediction. We selected the most optimal model based on the lowest misclassification error. Then the model was internally validated and tested with bootstrapping (1000x) and over optimism estimate as well as the adjusted AUC was calculated.
Results: TEM after one cycle of R-CHOP revealed abundant particles < 200 nm and TRPS measured significantly higher particle concentration in EV-enriched fractions. Plasma EVs were positive for CD63, CD81, flotillin-1, syntenin, HSP70, and negative for calnexin as determined by WB in accordance with the Minimal Information for Studies of EVs (MISEV) criteria 2018 for EV characterization. The most optimal model was an Elastic Net regression (a = 0.4) model consisting of 199 miRNAs with an area under the curve (AUC) of 0.95 (Confidence Interval (CI): 0.90 - 0.99) (Figure 1) [Sensitivity: 88%, Specificity: 90%; Positive Predictive Value (PPV): 90%, Negative Predictive Value (NPV): 87%]. We tested our model with bootstrapping (1,000x). After taking into account of over optimism estimate of 0.14, the adjusted AUC was 0.81 (CI: 0.64-0.96), which is higher than the performance of interim PET/CT [Sensitivity: 33-87%, Specificity: 49-94%; PPV: 20-74%, NPV: 64-95%] (Burggraaff 2019, PMID: 30141066).
Conclusion: Machine learning models using plasma EV-miRNAs prepared with the IsoSeek small RNA sequencing protocol yielded a robust signature that can predict EOI response already after one cycle of R-CHOP with a NPV of 87% and a PPV of 90%. The next step is to validate this model in a large cohort of HGBL-DH/TH cases and explore its potential in all subtypes of diffuse large B-cell lymphoma. If validated in independent cohorts, this novel approach could potentially, in combination with other modalities such as cell-free DNA and interim PET-CT, guide early risk-adapted treatment strategies in aggressive high-grade B-cell lymphomas.

Gepubliceerd: Blood. 2022;140(Supplement 1):3523-4.
Impact factor: 22.669 ; Q1

39. Paediatric COVID-19 mortality: a database analysis of the impact of health resource disparity
Marwali EM, Kekalih A, Yuliarto S, Wati DK, Rayhan M, Valerie IC, Cho HJ, Jassat W, Blumberg L, Masha M, Semple C, Swann OV, Kohns Vasconcelos M, Popielska J, Murthy S, Fowler RA, Guerguerian AM, Streinu-Cercel A, Pathmanathan MD, Rojek A, Kartsonaki C, Goncalves BP, Citarella BW, Merson L, Olliaro PL, Dalton HJ, International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Clinical Characterization Group Investigators; Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H

Background: The impact of the COVID-19 pandemic on paediatric populations varied between high-income countries (HICs) versus low-income to middle-income countries (LMICs). We sought to investigate differences in paediatric clinical outcomes and identify factors contributing to disparity between countries.
Methods: The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) COVID-19 database was queried to include children under 19 years of age admitted to hospital from January 2020 to April 2021 with suspected or confirmed COVID-19 diagnosis. Univariate and multivariable analysis of contributing factors for mortality were assessed by country group (HICs vs LMICs) as defined by the World Bank criteria.
Results: A total of 12 860 children (3819 from 21 HICs and 9041 from 15 LMICs) participated in this study. Of these, 8961 were laboratory-confirmed and 3899 suspected COVID-19 cases. About 52% of LMICs children were black, and more than 40% were infants and adolescent. Overall in-hospital mortality rate (95% CI) was 3.3% [=(3.0% to 3.6%), higher in LMICs than HICs (4.0% (3.6% to 4.4%) and 1.7% (1.3% to 2.1%), respectively). There were significant differences between country income groups in intervention profile, with higher use of antibiotics, antivirals, corticosteroids, prone positioning, high flow nasal cannula, non-invasive and invasive mechanical ventilation in HICs. Out of the 439 mechanically ventilated children, mortality occurred in 106 (24.1%) subjects, which was higher in LMICs than HICs (89 (43.6%) vs 17 (7.2%) respectively). Pre-existing infectious comorbidities (tuberculosis and HIV) and some complications (bacterial pneumonia, acute respiratory distress syndrome and myocarditis) were significantly higher in LMICs compared with HICs. On multivariable analysis, LMIC as country income group was associated with increased risk of mortality (adjusted HR 4.73 (3.16 to 7.10)).
Conclusion: Mortality and morbidities were higher in LMICs than HICs, and it may be attributable to differences in patient demographics, complications and access to supportive and treatment modalities.

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Impact factor: 2.922; Q2

Totale impact factor: 662.640
Gemiddelde impact factor: 16.991

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 0
Gemiddelde impact factor: 0

Kaakchirurgie

1. Reliability of 3D Stereophotogrammetry for Measuring Postoperative Facial Swelling
Buitenhuis MB, Klijn RJ, Rosenberg A, Speksnijder CM.

This study aimed to determine the reliability of three-dimensional (3D) stereophotogrammetry as a measurement instrument for evaluating soft tissue changes in the head and neck area. Twelve patients received a bilateral sagittal split osteotomy (BSSO). Test and retest 3D photographs were captured within the first three postoperative weeks, and a reference 3D photograph was capture at three months postoperatively. Distance measurements, mean and root mean square of the distance map, and volume differences were obtained. Reliability of these parameters was assessed by intraclass correlation coefficients (ICCs), standard error of measurement (SEM), and smallest detectable change (SDC). All distance measurements had an ICC > 0.91, and the distance map parameters and volume differences showed ICCs > 0.89. The neck region presented the largest SEMs (5.09 mL) and SDC (14.1 mL) for the volume difference. In conclusion, 3D stereophotogrammetry is reliable for distance and volume measurements of soft tissues in patients after a BSSO advancement.

Gepubliceerd: J Clin Med. 2022;11(23).
Impact factor: 4.964 ; Q2

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2. Application and accuracy of ultrasound-guided resections of tongue cancer
de Koning KJ, van Es RJJ, Klijn RJ, Breimer GE, Willem Dankbaar J, Braunius WW, van Cann EM, Dieleman FJ, Rijken JA, Tijink BM, de Bree R, Noorlag R.

Objectives: Surgical removal of squamous cell carcinoma of the tongue (SCCT) with tumour-free margin status (≥5 mm) is essential for loco-regional control. Inadequate margins (<5 mm) often indicate adjuvant treatment, which results in increased morbidity. Ultrasound (US)-guided SCCT resection may be a useful technique to achieve more adequate resection margins compared to conventional surgery. This study evaluates the application and accuracy of this technique**.**
Methods: Forty patients with SCCT were included in a consecutive US cohort. During surgery, the surgeon aimed for a 10-mm echographic resection margin, while the tumour border and resection plane were captured in one image. Ex-vivo US measurements of the resection specimen determined whether there was a need for an immediate re-resection. The margin status and the administration of adjuvant treatment were compared those of with a consecutive cohort of 96 tongue cancer patients who had undergone conventional surgery. A receiver operating characteristic analysis was done to assess the optimal margin of ex-vivo US measurements to detect histopathologically inadequate margins**.**
Results: In the US cohort, the frequency of free margin status was higher than in the conventional cohort (55% vs. 16%, $p < 0.001$), and the frequency of positive margins status (<1 mm) was lower (5% vs. 15%, respectively, $p < 0.001$). Adjuvant radiotherapy was halved (10% vs. 21%), and the need for re-resection was comparable (10% vs. 9%). A cut-off value of 8 mm for ex-vivo measurements prevented histopathologically inadequate margins in 76%**.**
Conclusion: US-guided SCCT resections improve margin status and reduce the frequency of adjuvant radiotherapy.

Gepubliceerd: Oral Oncol. 2022;133:106023.
Impact factor: 5.972 ; Q1

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3. A Comprehensive Grading System for a Magnetic Sentinel Lymph Node Biopsy Procedure in Head and Neck Cancer Patients
Nieuwenhuis ER, Kolenaar B, Hof JJ, van Baarlen J, van Bemmel AJM, Christenhusz A, Scheenen TWJ, Ten Haken B, de Bree R, Alic L.

A magnetic sentinel lymph node biopsy ((SLN)B) procedure has recently been shown feasible in oral cancer patients. However, a grading system is absent for proper identification and classification, and thus for clinical reporting. Based on data from eight complete magnetic SLNB procedures, we propose a provisional grading system. This grading system includes: (1) a qualitative five-point grading scale for MRI evaluation to describe iron uptake by LNs; (2) an ex vivo count of resected SLN with a magnetic probe to quantify iron amount; and (3) a qualitative five-point grading scale for histopathologic examination of excised magnetic SLNs. Most SLNs with iron uptake were identified and detected in level II. In this level, most variance in grading was seen for MRI and histopathology; MRI and medullar sinus were especially highly graded, and cortical sinus was mainly low graded. On average 82 ± 58 µg iron accumulated in harvested SLNs, and there were no significant differences in injected tracer dose (22.4 mg or 11.2 mg iron). In conclusion, a first step was taken in defining a comprehensive grading system to gain more insight into the lymphatic draining system during a magnetic SLNB procedure.

Gepubliceerd: Cancers (Basel). 2022;14(3).
Impact factor: 6.575; Q1

Totale impact factor: 17.511
Gemiddelde impact factor: 5.837

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 11.539
Gemiddelde impact factor: 5.770

Kindergeneeskunde

1. Safety of Thioguanine in Pediatric Inflammatory Bowel Disease: A Multi-Center Case Series
Bayoumy AB, Jagt JZ, van Wering HM, de Ridder L, Hummel T, Wolters VM, Stapelbroek J, Benninga MA, Mulder CJJ, de Boer NKH, de Meij TGJ.

Objectives: Thioguanine (TG) has been shown as a safe alternative in adults with inflammatory bowel disease (IBD) who did not tolerate conventional thiopurines [azathioprine (AZA)/mercaptopurine]. However, data in pediatric IBD are scarce. Therefore, we aimed to assess the safety of TG as maintenance therapy**.**
Methods: A retrospective, multicenter cohort study of children with IBD on TG was performed in the Netherlands. TG-related adverse events (AE) were assessed and listed according to the common terminology criteria for AE**.**
Results: Thirty-six children with IBD (median age 14.5 years) on TG (median dose 15 mg/day) were included in 6 centers. Five AE occurred during follow-up [pancreatitis (grade 3), hepatotoxicity (grade 3) (n = 2), Clostridium difficile infection (grade 2), and abdominal pain (grade 2)]. All patients (n = 8) with a previously AZA-induced pancreatitis did not redevelop pancreatitis on TG.
Conclusions: In pediatric IBD, TG seems a safe alternative in case of AZA-induced pancreatitis. Further research assessing long-term TG-related safety and efficacy is needed.

Gepubliceerd: J Pediatr Gastroenterol Nutr. 2022;75(6):e111-e5.
Impact factor: 3.355 ; Q2

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2. Inflammatory responses in SARS-CoV-2 associated Multisystem Inflammatory Syndrome and Kawasaki Disease in children: An observational study
Biesbroek G, Kapitein B, Kuipers IM, Gruppen MP, van Stijn D, Peros TE, van Veenendaal M, Jansen MHA, van der Zee CW, van der Kuip M, von Asmuth EGJ, Mooij MG, den Boer MEJ, Landman GW, van Houten MA, Schonenberg-Meinema D, Tutu van Furth AM, Boele van Hensbroek M, Scherpbier H, van Meijgaarden KE, Ottenhoff THM, Joosten SA, Ketharanathan N, Blink M, Brackel CLH, Zaaijer HL, Hombrink P, van den Berg JM, Buddingh EP, Kuijpers TW.

Multisystem Inflammatory Syndrome in Children (MIS-C) is a severe inflammatory disease in children related to SARS-CoV-2 with multisystem involvement including marked cardiac dysfunction and clinical symptoms that can resemble Kawasaki Disease (KD). We hypothesized that MIS-C and KD might have commonalities as well as unique inflammatory responses and studied these responses in both diseases. In total, fourteen children with MIS-C (n=8) and KD (n=6) were included in the period of March-June 2020. Clinical and routine blood parameters, cardiac follow-up, SARS-CoV-2-specific antibodies and CD4+ T-cell responses, and cytokine-profiles were determined in both groups. In contrast to KD patients, all MIS-C patients had positive Spike protein-specific CD3+CD4+ T-cell responses. MIS-C and KD patients displayed marked hyper-inflammation with high expression of serum cytokines, including the drug-targetable interleukin (IL)-6 and IFN-γ associated chemokines CXCL9, 10 and 11, which decreased at follow-up. No statistical differences were observed between groups. Clinical outcomes were all favourable without cardiac sequelae at 6 months follow-up. In conclusion, MIS-C and KD-patients both displayed cytokine-associated hyper-inflammation with several high levels of drug-targetable cytokines.

Gepubliceerd: PLoS One. 2022;17(11):e0266336.
Impact factor: 3.752 ; Q2

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3. An Algorithm for Strategic Continuation or Restriction of Asthma Medication Prior to Exercise Challenge Testing in Childhood Exercise Induced Bronchoconstriction
Hengeveld VS, Keijzer PB, Diamant Z, Thio BJ.

Exercise induced bronchial (EIB) constriction is a common and highly specific feature of pediatric asthma and should be diagnosed with an exercise challenge test (ECT). The impact of EIB in asthmatic children's daily lives is immense, considering the effects on both physical and psychosocial development. Monitoring childhood asthma by ECT's can provide insight into daily life disease burden and the control of asthma. Current guidelines for bronchoprovocation tests restrict both the use of reliever and maintenance asthma medication before an exercise challenge to prevent false-negative testing, as both have significant acute bronchoprotective properties. However, restricting maintenance medication before an ECT may be less appropiate to evaluate EIB symptoms in daily life when a diagnosis of asthma is well established. Rigorous of maintenance medication before an ECT according to guidelines may lead to overestimation of the real, daily life asthma burden and lead to an inappropiate step-up in therapy. The protection against EIB offered by the combined acute and chronic bronchoprotective effects of maintenance medication can be properly assessed whilst maintaining them. This may aid in achieving the goal of unrestricted participation of children in daily play and sports activities with their peers without escalation of therapy. When considering a step down in medication, a strategic wash-out of maintenance medication before an ECT aids in providing objective support of potential discontinuation of maintenance medication.

Gepubliceerd: Front Pediatr. 2022;10:800193.
Impact factor: 3.569 ; Q2

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4. Can the response to a single dose of beclomethasone dipropionate predict the outcome of long-term treatment in childhood exercise-induced bronchoconstriction?
Hengeveld VS, Lammers N, van der Kamp MR, van der Palen J, Thio BJ.

Background: Exercise-induced bronchoconstriction (EIB) is a frequent and highly specific symptom of childhood asthma. Inhaled corticosteroids (ICS) are the mainstay of controller therapy for EIB and asthma; however, a proportion of asthmatic children and adolescents is less responsive to ICS. We hypothesized that a single dose response to ICS could function as a predictor for individual long-term efficacy of ICS.
Objective: To assess the predictive value of the bronchoprotective effect of a single-dose beclomethasone dipropionate (BDP) against EIB for the bronchoprotective effect of 4 weeks of treatment, using an exercise challenge test (ECT)**.**
Methods: Thirty-two steroid-naïve children and adolescents aged 6 to 18 years with EIB were included in this prospective cohort study. They performed an ECT at baseline, after a single-dose BDP (200µg) and after 4 weeks of BDP treatment (100 µg twice daily) to assess EIB severity**.**
Results: The response to a single-dose BDP on exercise-induced fall in FEV1 showed a significant correlation with the response on exercise-induced fall in FEV1 after 4 weeks of BDP treatment ($r = .38$, $p = .004$). A reduction in post-exercise fall in FEV1 of more than 8% after a single-dose BDP could predict BDP efficacy against EIB after 4 weeks of treatment with a positive predictive value of 100% (CI: 86.1-100%) and a negative predictive value of 29.4% (CI: 11.7%-53.7%)**.**
Conclusion: We found that the individual response to a single-dose BDP against EIB has a predictive value for the efficacy of long-term treatment with BDP. This could support clinicians in providing personalized management of EIB in childhood asthma.

Gepubliceerd: Pediatr Allergy Immunol. 2022;33(6):e13808.
Impact factor: 2.676 ; Q1

5. First-line treatment with infliximab versus conventional treatment in children with newly diagnosed moderate-to-severe Crohn's disease: an open-label multicentre randomised controlled trial

Jongsma MME, Aardoom MA, Cozijnsen MA, van Pieterson M, de Meij T, Groeneweg M, Norbruis OF, Wolters VM, van Wering HM, Hojsak I, Kolho KL, Hummel T, Stapelbroek J, van der Feen C, van Rheenen PF, van Wijk MP, Teklenburg-Roord STA, Schreurs MWJ, Rizopoulos D, Doukas M, Escher JC, Samsom JN, de Ridder L.

Objective: In newly diagnosed paediatric patients with moderate-to-severe Crohn's disease (CD), infliximab (IFX) is initiated once exclusive enteral nutrition (EEN), corticosteroid and immunomodulator therapies have failed. We aimed to investigate whether starting first-line IFX (FL-IFX) is more effective to achieve and maintain remission than conventional treatment.
Design: In this multicentre open-label randomised controlled trial, untreated patients with a new diagnosis of CD (3-17 years old, weighted Paediatric CD Activity Index score (wPCDAI) >40) were assigned to groups that received five infusions of 5 mg/kg IFX at weeks 0, 2, 6, 14 and 22 (FL-IFX), or EEN or oral prednisolone (1 mg/kg, maximum 40 mg) (conventional). The primary outcome was clinical remission on azathioprine, defined as a wPCDAI <12.5 at week 52, without need for treatment escalation, using intention-to-treat analysis**.**
Results: 100 patients were included, 50 in the FL-IFX group and 50 in the conventional group. Four patients did not receive treatment as per protocol. At week 10, a higher proportion of patients in the FL-IFX group than in the conventional group achieved clinical (59% vs 34%, respectively, p=0.021) and endoscopic remission (59% vs 17%, respectively, p=0.001). At week 52, the proportion of patients in clinical remission was not significantly different (p=0.421). However, 19/46 (41%) patients in the FL-IFX group were in clinical remission on azathioprine monotherapy without need for treatment escalation vs 7/48 (15%) in the conventional group (p=0.004).
Conclusions: FL-IFX was superior to conventional treatment in achieving short-term clinical and endoscopic remission, and had greater likelihood of maintaining clinical remission at week 52 on azathioprine monotherapy.
Trial registration number: ClinicalTrials.gov Registry (NCT02517684).

Gepubliceerd: Gut. 2022;71(1):34-42.
Impact factor: 31.795 Q1

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6. Efficacy and safety of switching from intravenous to oral antibiotics (amoxicillin-clavulanic acid) versus a full course of intravenous antibiotics in neonates with probable bacterial infection (RAIN): a multicentre, randomised, open-label, non-inferiority trial

Keij FM, Kornelisse RF, Hartwig NG, van der Sluijs-Bens J, van Beek RHT, van Driel A, van Rooij LGM, van Dalen-Vink I, Driessen GJA, Kenter S, von Lindern JS, Eijkemans M, Stam-Stigter GM, Qi H, van den Berg MM, Baartmans MGA, van der Meer-Kappelle LH, Meijssen CB, Norbruis OF, Heidema J, van Rossem MC, den Butter PCP, Allegaert K, Reiss IKM, Tramper-Stranders GA.

Background: Switching from intravenous antibiotic therapy to oral antibiotic therapy among neonates is not yet practised in high-income settings due to uncertainties about exposure and safety. We aimed to assess the efficacy and safety of early intravenous-to-oral antibiotic switch therapy compared with a full course of intravenous antibiotics among neonates with probable bacterial infection**.**
Methods: In this multicentre, randomised, open-label, non-inferiority trial, patients were recruited at 17 hospitals in the Netherlands. Neonates (postmenstrual age ≥35 weeks, postnatal age 0-28 days,

bodyweight ≥2 kg) in whom prolonged antibiotic treatment was indicated because of a probable bacterial infection, were randomly assigned (1:1) to switch to an oral suspension of amoxicillin 75 mg/kg plus clavulanic acid 18·75 mg/kg (in a 4:1 dosing ratio, given daily in three doses) or continue on intravenous antibiotics (according to the local protocol). Both groups were treated for 7 days. The primary outcome was cumulative bacterial reinfection rate 28 days after treatment completion. A margin of 3% was deemed to indicate non-inferiority, thus if the reinfection rate in the oral amoxicillin-clavulanic acid group was less than 3% higher than that in the intravenous antibiotic group the null hypothesis would be rejected. The primary outcome was assessed in the intention-to-treat population (ie, all patients who were randomly assigned and completed the final follow-up visit on day 35) and the per protocol population. Safety was analysed in all patients who received at least one administration of the allocated treatment and who completed at least one follow-up visit. Secondary outcomes included clinical deterioration and duration of hospitalisation. This trial was registered with ClinicalTrials.gov, NCT03247920, and EudraCT, 2016-004447-36**.**
Findings: Between Feb 8, 2018 and May 12, 2021, 510 neonates were randomly assigned (n=255 oral amoxicillin-clavulanic group; n=255 intravenous antibiotic group). After excluding those who withdrew consent (n=4), did not fulfil inclusion criteria (n=1), and lost to follow-up (n=1), 252 neonates in each group were included in the intention-to-treat population. The cumulative reinfection rate at day 28 was similar between groups (one [<1%] of 252 neonates in the amoxicillin-clavulanic acid group vs one [<1%] of 252 neonates in the intravenous antibiotics group; between-group difference 0 [95% CI -1·9 to 1·9]; p(non-inferiority)<0·0001). No statistically significant differences were observed in reported adverse events (127 [50%] vs 113 [45%]; p=0·247). In the intention-to-treat population, median duration of hospitalisation was significantly shorter in the amoxicillin-clavulanic acid group than the intravenous antibiotics group (3·4 days [95% CI 3·0-4·1] vs 6·8 days [6·5-7·0]; p<0·0001).
Interpretation: An early intravenous-to-oral antibiotic switch with amoxicillin-clavulanic acid is non-inferior to a full course of intravenous antibiotics in neonates with probable bacterial infection and is not associated with an increased incidence of adverse events. FUNDING: The Netherlands Organization for Health Research and Development, Innovatiefonds Zorgverzekeraars, and the Sophia Foundation for Scientific Research.

Gepubliceerd: Lancet Child Adolesc Health. 2022;6(11):799-809.
Impact factor: 37.746 ; Q1

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7. A neonate with a facial congenital pressure injury: a case report
van der Sluis N, Theodora Wilhelmina Ten Hoope B, Bosch T, Wiesman ME, Schmidbauer U, Rakhorst HA.

This is the first case report of a facial congenital pressure injury in a full-term neonate, due to pressure on the neonate's head between a large leiomyoma and the mother's pelvic bone.

Gepubliceerd: Case Reports Plast Surg Hand Surg. 2022;9(1):88-91.
Impact factor: 0 ; Q NVT

Totale impact factor: 82.893
Gemiddelde impact factor: 11.842

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 6.245
Gemiddelde impact factor: 3.123

Klinische chemie

1. Assessment of Comorbidity in Bariatric Patients through a Biomarker-Based Model-A Multicenter Validation of the Metabolic Health Index
Gensen C, van Loon SLM, van Riel NA, Nienhuijs S, Triepels R, Kos S, Mulder AHL, Pouw N, Scharnhorst V, Boer AK.

Background: The metabolic health index (MHI) is a biomarker-based model that objectively assesses the cumulative impact of comorbidities type 2 diabetes mellitus, hypertension and dyslipidemia on the health state of bariatric patients. The MHI was developed on a single-center cohort using a fully laboratory data-driven approach, resulting in a MHI score on a range from 1 to 6. To show universal applicability in clinical care, the MHI was validated externally and potential laboratory-related shortcomings were evaluated**.**
Methods: Retrospective laboratory and national bariatric quality registry data were collected from five Dutch renowned bariatric centers (n = 11 501). MHI imprecision was derived from the cumulative effect of biological and analytical variance of the individual input variables of the MHI model. The performance of the MHI (model) was assessed in terms of discrimination and calibration**.**
Results: The cumulative imprecision in MHI was 0.25 MHI points. Calibration of the MHI model diverged over the different centers but was accounted for by misregistration of comorbidity after cross-checking the data. Discriminative performance of the MHI model was consistent across the different centers.
Conclusions: The MHI model can be applied in clinical practice of bariatric centers, regardless of patient mix and analytical platform. Because the MHI is based on objective parameters, it is insensitive to diverging clinical definitions of comorbidities. Therefore, the MHI can be used to objectify severity of metabolic comorbidities in bariatric patients. The MHI can support the patient-selection process for surgery and objectively assessing the effect of surgery on the metabolic health state.

Gepubliceerd: J Appl Lab Med. 2022;7(5):1062-75.
Impact factor: 0 ; Q NVT

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2. Impact of Preanalytical Factors on Calprotectin Concentration in Stool: A Multiassay Comparison
Hamer HM, Mulder AHL, de Boer NK, Crouwel F, van Rheenen PF, Spekle M, Vermeer M, Wagenmakers-Huizinga L, Muller Kobold AC.

Background: Measuring calprotectin concentration in stool is increasingly important in monitoring disease activity and treatment response in inflammatory bowel disease. This study evaluates the impact of preanalytical storage conditions on reliability of calprotectin testing using 5 different calprotectin immunoassays**.**
Methods: Aliquots of homogenized fresh fecal samples in untreated or extracted form were stored at room temperature or 4 degrees C. Calprotectin concentration was measured day 0 to 4 and 8. Five different immunoassays and accompanying extraction buffers were used (CALiaGold, Phadia EliA, Buhlmann fCal turbo, ELISA Buhlmann, Inova Quanta Flash). Repeated measurements of change from baseline calprotectin levels over time were analyzed using a mixed model analysis**.**
Results: Calprotectin concentrations declined over time under all preanalytical conditions with all assays, except for extracted feces stored at 4 degrees C. The rate of decline was greatest in untreated stool kept at room temperature, reaching significant difference from baseline already after 1 day (P < 0.001). In extracted feces kept at room temperature, significant difference from baseline was reached after 2 days, and in untreated feces at 4 degrees C, after 4 days. However, the results

differed significantly between assays. After 4 days of storage at room temperature, the mean calprotectin decline from baseline differed between 30% and 60%, dependent on the assay used. **Conclusions:** Fecal calprotectin concentration in stool samples declines over time, and the rate of decline is greater at higher temperatures. In extracted feces stored at 4 degrees C, calprotectin is most stable. It is assay-dependent how long extracted feces stored at 4 degrees C give reliable test results.

Gepubliceerd: J Appl Lab Med. 2022;7(6):1401-11.
Impact factor: 0 ; Q NVT

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3. High Titers of Low Affinity Antibodies in COVID-19 Patients Are Associated With Disease Severity
Hendriks J, Schasfoort R, Koerselman M, Dannenberg M, Cornet AD, Beishuizen A, van der Palen J, Krabbe J, Mulder AHL, Karperien M.

Background: Almost 2 years from the beginning of the coronavirus disease 2019 (COVID-19) pandemic, there is still a lot unknown how the humoral response affects disease progression. In this study, we investigated humoral antibody responses against specific SARS-CoV2 proteins, their strength of binding, and their relationship with COVID severity and clinical information. Furthermore, we studied the interactions of the specific receptor-binding domain (RBD) in more depth by characterizing specific antibody response to a peptide library.
Material and Methods: We measured specific antibodies of isotypes IgM, IgG, and IgA, as well as their binding strength against the SARS-CoV2 antigens RBD, NCP, S1, and S1S2 in sera of 76 COVID-19 patients using surface plasmon resonance imaging. In addition, these samples were analyzed using a peptide epitope mapping assay, which consists of a library of peptides originating from the RBD**.**
Results: A positive association was observed between disease severity and IgG antibody titers against all SARS-CoV2 proteins and additionally for IgM and IgA antibodies directed against RBD. Interestingly, in contrast to the titer of antibodies, the binding strength went down with increasing disease severity. Within the critically ill patient group, a positive association with pulmonary embolism, d-dimer, and antibody titers was observed**.**
Conclusion: In critically ill patients, antibody production is high, but affinity is low, and maturation is impaired. This may play a role in disease exacerbation and could be valuable as a prognostic marker for predicting severity.

Gepubliceerd: Front Immunol. 2022;13:867716.
Impact factor: 8.787 ; Q1

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4. Automated prediction of low ferritin concentrations using a machine learning algorithm
Kurstjens S, de Bel T, van der Horst A, Kusters R, Krabbe J, van Balveren J.

Objectives: Computational algorithms for the interpretation of laboratory test results can support physicians and specialists in laboratory medicine. The aim of this study was to develop, implement and evaluate a machine learning algorithm that automatically assesses the risk of low body iron storage, reflected by low ferritin plasma levels, in anemic primary care patients using a minimal set of basic laboratory tests, namely complete blood count and C-reactive protein (CRP)**.**
Methods: Laboratory measurements of anemic primary care patients were used to develop and validate a machine learning algorithm. The performance of the algorithm was compared to twelve specialists in laboratory medicine from three large teaching hospitals, who predicted if patients with anemia have low ferritin levels based on laboratory test reports (complete blood count and CRP). In a

second round of assessments the algorithm outcome was provided to the specialists in laboratory medicine as a decision support tool**.**
Results: Two separate algorithms to predict low ferritin concentrations were developed based on two different chemistry analyzers, with an area under the curve of the ROC of 0.92 (Siemens) and 0.90 (Roche). The specialists in laboratory medicine were less accurate in predicting low ferritin concentrations compared to the algorithms, even when knowing the output of the algorithms as support tool. Implementation of the algorithm in the laboratory system resulted in one new iron deficiency diagnosis on average per day.
Conclusions: Low ferritin levels in anemic patients can be accurately predicted using a machine learning algorithm based on routine laboratory test results. Moreover, implementation of the algorithm in the laboratory system reduces the number of otherwise unrecognized iron deficiencies.

Gepubliceerd: Clin Chem Lab Med. 2022;60(12):1921-8.
Impact factor: 8.490; Q1

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5. External quality assessment of flow cytometric bronchoalveolar lavage cellular analysis: 20 years' experience in The Netherlands
Mulder AHL, Eidhof HHM, Gratama JW.

Background: Bronchoalveolar (BAL) cellular analysis can be supportive in the diagnosis of interstitial lung disease. The flow cytometric analysis of BAL fluid cells is complicated by cell fragility and adherence and autofluorescence of macrophages, making conventional analysis of BAL fluid cells as done in external quality schemes (EQA) for blood lymphocyte subsets, not representative. Following a procedure for stabilized BAL cells, a separate EQA was set up. The results of 20 years' experience are presented**.**
Methods: From each round between 2000 and 2020 the following flow cytometric parameters were recorded from each participant: total lymphocyte population (TLY), CD3+ lymphocytes, CD3+ CD4+ lymphocytes, CD3+ CD8+ lymphocytes, CD3- CD16+/56+ lymphocytes, CD19+ lymphocytes and CD103 + CD3+ lymphocytes. In addition, the eosinophils and neutrophils were recorded. The mean and standard deviation of each parameter per round were calculated. The 40 rounds were divided in four respective groups of 10 in order to compare the results as function of time. In addition the interpretation of the results of participants was scored**.**
Results: The median SD in the four groups was below 10% for all parameters except for TLY and the CD103+ CD3+ lymphocytes. No improvement in time was observed for any (sub)population except for the CD3+ CD4+ subset. Interpretation of the results varied based on disease, with greatest consensus for sarcoidosis cases and lowest for nonspecific interstitial lung disease cases.
Conclusions: A dedicated EQA for BAL fluid cellular analysis appears to be justified as the test material is substantially different from that of peripheral blood. We show that adequate analytical and post-analytical quality control can be achieved.

Gepubliceerd: Cytometry B Clin Cytom. 2022;102(6):451-7.
Impact factor: 3.248; Q2

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6. Hypothyroid Symptoms Throughout Pregnancy Are Predominantly Associated with Thyroxine and Not with Thyrotropin Concentrations
Pop VJ, Hulsbosch LP, Boekhorst M, Broeren MAC, Krabbe JG, Wiersinga WM.

Background: It is unclear whether levels of hypothyroid symptoms in pregnant women with (sub)clinical thyroid dysfunction differ from euthyroid controls and whether free thyroxine

(fT4)/thyrotropin (TSH) changes throughout pregnancy affect hypothyroid symptom levels. The objective was twofold: (1) To compare hypothyroid symptom levels between thyroid dysfunction subgroups and a carefully defined reference group; (2) to assess the association between fT4/TSH changes throughout pregnancy and hypothyroid symptom levels adjusted for depressive symptoms**.**
Methods: The current study was a longitudinal prospective cohort study in 1800 healthy pregnant women. At each trimester of pregnancy, hypothyroid symptoms were assessed with a 12-item symptom hypothyroidism checklist and depressive symptoms with the Edinburgh Depression Scale. Thyroid dysfunction was defined using the 2.5-97.5th fT4/TSH percentile of thyroid peroxidase antibodies-negative women. Euthyroid controls consisted of women with appropriate fT4 levels within the 10-90th percentile and with a normal TSH level. Hypothyroid symptom mean scores were compared between controls and several thyroid dysfunction subgroups. Growth mixture modeling was performed to evaluate possible longitudinal trajectories of hypothyroid and depressive symptoms. The association between hypothyroid symptom trajectories (adjusted for depression) and fT4/TSH changes was assessed with multivariate logistic regression analysis**.**
Results: Women with overt hypothyroidism (fT4 < 2.5th, TSH >97.5th) and hypothyroxinemia (fT4 < 2.5th, TSH: 2.5-97.5th) showed higher hypothyroid symptom levels compared with the euthyroid controls and women with subclinical hypothyroidism (SCH, fT4: 2.5-97.5th, TSH >97.5th), because 82% of these SCH women had fT4 levels in the euthyroid range. Two groups of hypothyroid and depressive symptoms were defined: a persistently low and persistently high symptom group. fT4 decreased in 98% of the women from the first to third trimester and per unit pmol/L fT4 decrease (not TSH increase), the likelihood to present persistently high hypothyroid symptoms increased with 46%, adjusted for depression**.**
Conclusions: A properly defined euthyroid control group distinguishes women with hypothyroid symptoms. An fT4 decrease toward end term is associated with persistently high hypothyroid symptom levels. Clinicians should be aware of the importance of fT4 stratification in SCH women.

Gepubliceerd: Thyroid. 2022;32(10):1249-58.
Impact factor: 6.506 ; Q1

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7. Delayed Diagnosis of Severe Hypoglycemia in a Septic Patient With Chronic Renal Failure
Ten Berge D, Manning F, Silderhuis V, Deijns S, Pouwels MJ, Krabbe H, Beishuizen A.

High-dose vitamin C therapy has gained increased interest as an adjunctive treatment of septic shock, although convincing evidence is still lacking. High blood levels of vitamin C may interfere with several point-of-care blood glucose meters. We describe the case of a 67-year-old septic patient known with chronic renal failure who developed truly severe hypoglycemia, which was masked by spuriously high glucose values measured on a capillary blood glucose meter. This initially led to the treatment of spurious hyperglycemia with high-dose insulin and a delayed correct diagnosis and treatment, rendering substantial risk for the patient. Awareness of this dangerous interference is warranted.

Gepubliceerd: Cureus. 2022;14(8):e28615.
Impact factor: 0 ; Q NVT

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8. Added value of drug-laboratory test interaction alerts in test result authorisation
van Balveren JA, Verboeket-van de Venne W, Doggen CJM, Erdem-Eraslan L, de Graaf AJ, Krabbe JG, Musson REA, Oosterhuis WP, de Rijke YB, van der Sijs H, Tintu AN, Verheul RJ, Hoedemakers RMJ, Kusters R.

Gepubliceerd: Clin Chem Lab Med. 2022;60(5):e108-e11.
Impact factor: 8.490; Q1

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9. Real-time monitoring of drug laboratory test interactions: a proof of concept
van Balveren JA, Verboeket-van de Venne W, Doggen CJM, Erdem-Eraslan L, de Graaf AJ, Krabbe JG, Musson REA, Oosterhuis WP, de Rijke YB, van der Sijs H, Tintu AN, Verheul RJ, Hoedemakers RMJ, Kusters R.

Objectives: For the correct interpretation of test results, it is important to be aware of drug-laboratory test interactions (DLTIs). If DLTIs are not taken into account by clinicians, erroneous interpretation of test results may lead to a delayed or incorrect diagnosis, unnecessary diagnostic testing or therapy with possible harm for patients. A DLTI alert accompanying a laboratory test result could be a solution. The aim of this study was to test a multicentre proof of concept of an electronic clinical decision support system (CDSS) for real-time monitoring of DLTIs**.**
Methods: CDSS was implemented in three Dutch hospitals. So-called 'clinical rules' were programmed to alert medical specialists for possible DLTIs based on laboratory test results outside the reference range in combination with prescribed drugs. A selection of interactions from the DLTI database of the Dutch society of clinical chemistry and laboratory medicine were integrated in 43 clinical rules, including 24 tests and 25 drugs. During the period of one month all generated DTLI alerts were registered in the laboratory information system**.**
Results: Approximately 65 DLTI alerts per day were detected in each hospital. Most DLTI alerts were generated in patients from the internal medicine and intensive care departments. The most frequently reported DLTI alerts were potassium-proton pump inhibitors (16%), potassium-beta blockers (11%) and creatine kinase-statins (11%).
Conclusions: This study shows that it is possible to alert for potential DLTIs in real-time with a CDSS. The CDSS was successfully implemented in three hospitals. Further research must reveal its usefulness in clinical practice.

Gepubliceerd: Clin Chem Lab Med. 2022;60(2):235-42.
Impact factor: 8.490; Q1

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10. Added value of antiphosphatidylserine/prothrombin antibodies in the workup of thrombotic antiphospholipid syndrome: Communication from the ISTH SSC Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibodies
Vandevelde A, Chayoua W, de Laat B, Moore GW, Musiał J, Zuily S, Wahl D, Devreese KMJ.

Background: Diagnosis of antiphospholipid syndrome (APS) requires persistent presence of lupus anticoagulant (LAC), anticardiolipin (aCL) IgG/IgM, or anti-β2 glycoprotein I (aβ2GPI) IgG/IgM antibodies. Other antiphospholipid antibodies (aPL) such as antiphosphatidylserine/prothrombin antibodies (aPS/PT) are promising in assessment of thrombotic APS (TAPS).
Aim: To evaluate the added value of aPS/PT IgG and IgM in TAPS.
Material and Methods: aPS/PT IgG/IgM, aCL IgG/IgM, aβ2GPI IgG/IgM, and LAC were determined in 757 patients (TAPS and controls). aPS/PT cut-off values were calculated, and aPS/PT titers and positivity were compared between TAPS and controls, type of thrombosis, and antibody profiles. Likelihood ratios (LR), odds ratios (OR), and aPL score were determined**.**
Results: aPS/PT IgG and IgM were associated with TAPS and triple positivity. In-house calculated cut-offs were higher for IgM (43 units), compared to manufacturer's cut-off (30 units). Thresholds of 90 (IgG) and 200 (IgM) units were determined as high-titer cut-off. Higher aPS/PT titers were observed in triple positive patients and showed higher LR and OR for TAPS. aPS/PT was independently

associated with TAPS when adjusted for aCL/aβ2GPI, but not when adjusted for LAC. In isolated LAC positive patients, aPS/PT was positive in 27.1% TAPS patients and in 77.3% patients with autoimmune disease. Diagnostic value of aPL score did not differ with and without including aPS/PT**.**
Conclusion: aPS/PT positivity, especially with high antibody titer, is associated with TAPS diagnosis. Analysis on top of current laboratory criteria is not essential in TAPS diagnosis, but aPS/PT could be useful in patients with thrombosis and a double positive aPL profile (aCL+/aβ2GPI+).

Gepubliceerd: J Thromb Haemost. 2022;20(9):2136-50.
Impact factor: 16.041 ; Q1

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11. Lupus anticoagulant associates with thrombosis in patients with COVID-19 admitted to intensive care units: A retrospective cohort study
Noordermeer T, Schutgens REG, Visser C, Rademaker E, de Maat MPM, Jansen AJG, Limper M, Cremer OL, Kruip M, Endeman H, Maas C, de Laat B, Urbanus RT, Dutch COVID & Thrombosis Coalition (DCTC): Beishuizen A, Cornet AD, Krabbe J.

Background: Thrombosis is a frequent and severe complication in patients with coronavirus disease 2019 (COVID-19) admitted to the intensive care unit (ICU). Lupus anticoagulant (LA) is a strong acquired risk factor for thrombosis in various diseases and is frequently observed in patients with COVID-19. Whether LA is associated with thrombosis in patients with severe COVID-19 is currently unclear.
Objective: To investigate if LA is associated with thrombosis in critically ill patients with COVID-19.
Patients/methods: The presence of LA and other antiphospholipid antibodies was assessed in patients with COVID-19 admitted to the ICU. LA was determined with dilute Russell's viper venom time (dRVVT) and LA-sensitive activated partial thromboplastin time (aPTT) reagents**.**
Results: Of 169 patients with COVID-19, 116 (69%) tested positive for at least one antiphospholipid antibody upon admission to the ICU. Forty (24%) patients tested positive for LA; of whom 29 (17%) tested positive with a dRVVT, 19 (11%) tested positive with an LA-sensitive aPTT, and 8 (5%) tested positive on both tests. Fifty-eight (34%) patients developed thrombosis after ICU admission. The odds ratio (OR) for thrombosis in patients with LA based on a dRVVT was 2.5 (95% confidence interval [CI], 1.1-5.7), which increased to 4.5 (95% CI, 1.4-14.3) in patients at or below the median age in this study (64 years). LA positivity based on a dRVVT or LA-sensitive aPTT was only associated with thrombosis in patients aged less than 65 years (OR, 3.8; 95% CI, 1.3-11.4) and disappeared after adjustment for C-reactive protein**.**
Conclusion: Lupus anticoagulant on admission is strongly associated with thrombosis in critically ill patients with COVID-19, especially in patients aged less than 65 years.

Gepubliceerd: Res Pract Thromb Haemost. 2022;6(6):e12809.
Impact factor: 5.953 ; Q1

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12. Strategies for low-molecular-weight heparin management in pregnant women with mechanical prosthetic heart valves: A nationwide survey of Dutch practice
Voortman M, Roos JW, Slomp J, van Dijk APJ, Bouma BJ, Sieswerda GTJ, Kiès P, Boer A, Waskowski WM, von Birgelen C, Wagenaar LJ.

Background: In this study we investigated current Dutch practice of low molecular weight heparin (LMWH) treatment in pregnant women with mechanical prosthetic heart valves (MPHV) in order to evaluate how management can be optimized.

Methods: Between December 2020 and February 2021, we conducted a survey among Dutch congenital cardiologists of tertiary centers in the Netherlands. We collected and analyzed written, unstructured, open questionnaires that were send to all 8 specialized pregnancy heart teams.
Results: Response was obtained from all centers (response rate 100%). The preferred LMWHs were nadroparin (62.5%), dalteparin (25%), and enoxaparin (12.5%). After replacing vitamin K antagonist (VKA) with LMWH, 7 centers measured the first anti-Xa level within a week, and 1 center measured anti-Xa levels daily until targeted levels were reached. All centers monitored weekly peak anti-Xa levels (4–6 h post-dose) throughout pregnancy. Four out of 8 centers monitored additional trough (i.e. pre-dose) anti-Xa levels, and 3 of these 4 centers switched to LMWH 3 times daily to achieve target levels when necessary.
Conclusions: In Dutch clinical practice, a considerable variation exists in LMWH management for pregnant women with MPHV. In some centers, LMWH was dosed 3 times daily to maintain target anti-Xa levels. Standardizing treatment strategies would allow systematic assessment in prospective studies.

Gepubliceerd: International Journal of Cardiology Congenital Heart Disease. 2022;9:100676.
Impact Factor: 0; NVT

Totale impact factor: 66.005
Gemiddelde impact factor: 5.500

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 19.289
Gemiddelde impact factor: 9.645

Klinische farmacie

1. Population pharmacokinetic model and limited sampling strategy for clozapine using plasma and dried blood spot samples
Geers LM, Cohen D, Wehkamp LM, van Wattum HJ, Kosterink JGW, Loonen AJM, Touw DJ.

Background: To improve efficacy, therapeutic drug monitoring is often used in clozapine therapy. Trough level monitoring is regular, but trough levels provide limited information about the pharmacokinetics of clozapine and exposure in time. The area under the concentration time curve (AUC) is generally valued as better marker of drug exposure in time but calculating AUC needs multiple sampling. An alternative approach is a limited sampling scheme in combination with a population pharmacokinetic model meant for Bayesian forecasting. Furthermore, multiple venepunctions can be a burden for the patient, whereas collecting samples by means of dried blood spot (DBS) sampling can facilitate AUC-monitoring, making it more patient friendly.
Objective: Development of a population pharmacokinetic model and limited sampling strategy for estimating AUC(0-12h) (a twice-daily dosage regimen) and AUC(0-24h) (a once-daily dosage regimen) of clozapine, using a combination of results from venepunctions and DBS sampling.
Method: From 15 schizophrenia patients, plasma and DBS samples were obtained before administration and 2, 4, 6, and 8 h after clozapine intake. MwPharm(®) pharmacokinetic software was used to parameterize a population pharmacokinetic model and calculate limited sampling schemes**.**
Results: A three-point sampling strategy with samples at 2, 6, and 8 h after clozapine intake gave the best estimation of the clozapine AUC(0-12h) and at 4, 10, and 11 h for the AUC(0-24h). For clinical practice, however, a two-point sampling strategy with sampling points at 2 and 6 h was sufficient to estimate AUC(0-12h) and at 4 and 11 h for AUC(0-24h)**.**
Conclusion: A pharmacokinetic model with a two-time point limited sampling strategy meant for Bayesian forecasting using DBS sampling gives a better prediction of the clozapine exposure in time, expressed as AUC, compared to trough level monitoring. This limited sampling strategy might therefore provide a more accurate prediction of effectiveness and occurrence of side effects compared to trough level monitoring. The use of DBS samples also makes the collection of clozapine samples easier and wider applicable.

Gepubliceerd: Ther Adv Psychopharmacol. 2022;12:20451253211065857.
Impact factor: 4.988 ; Q2

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2. The QT interval prolongation potential of anticancer and supportive drugs: a comprehensive overview
Giraud EL, Ferrier KRM, Lankheet NAG, Desar IME, Steeghs N, Beukema RJ, van Erp NP, Smolders EJ.

Patients with cancer are prone to prolongation of the corrected QT interval (QTc) due to the use of anticancer drugs with QTc-prolonging potential in combination with electrolyte imbalances caused by, for example, gastrointestinal side-effects. However, most anticancer drugs were approved with little information on their QTc-prolonging potential and the added risk of torsade de pointes. The absence of this information on the drug label poses a considerable challenge to clinicians regarding the measures that need to be taken to safely start anticancer treatment. In this Review, we provide a comprehensive overview of the evidence for the QTc-prolonging properties of 205 anticancer drugs and 14 antiemetic drugs available from drug labels, assessment reports, and published studies. We classify the drugs as low-risk, moderate-risk, or high-risk for QTc prolongation. We also discuss the clinical relevance of these findings and include practical recommendations to guide clinicians to

select the drugs with the least QTc-prolonging properties and to adequately monitor susceptible patients.

Gepubliceerd: Lancet Oncol. 2022;23(9):e406-e15.
Impact factor: 54.433 ; Q1

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3. Pharmacokinetics of 2 oral paracetamol formulations in hospitalized octogenarians
Hias J, Van der Linden L, Walgraeve K, Gijsen M, Mian P, Koch BCP, Allegaert K, Annaert P, Tournoy J, Spriet I.

Aims: It is currently unclear how paracetamol should be dosed in order to increase its efficacy while warranting safety in very old adults. The objective was to evaluate the pharmacokinetics of 2 oral paracetamol formulations and its metabolites in hospitalized octogenarians.
Methods: Geriatric inpatients aged 80 years and older received a 1000-mg paracetamol tablet or granulate at 08.00, 14.00 and 20.00. After at least 4 consecutive gifts, plasma samples were collected around the 08.00 dose (trough, +0.5, +1, +2, +4, +5 and +6 h). Plasma concentrations of paracetamol and its metabolites were determined and individual pharmacokinetic parameters were derived. The Edmonton Frail Scale was used to assess frailty. An analgesic plasma target was defined as an average plasma concentration (C(avg)) of 10 mg/L.
Results: The mean (±standard deviation) age was 86.78 (±4.20) years. The majority (n = 26/36, 72%) received the tablet, 10 (28%) the granulate. Thirty patients (85%) were classified with moderate to severe frailty. Seven (21%) patients had a C(avg) above 10 mg/L. The median [interquartile range] time to reach the peak concentration was 50.5 [31.50-92.50] and 42.50 [33.75-106.75] min for the tablet and granulate, respectively. The coefficient of variation was 95% for time to reach the peak concentration and 30% for C(avg) of paracetamol. A correlation of C(avg) of paracetamol was observed with female sex and total serum bilirubin.
Conclusion: Large interindividual differences were found for pharmacokinetic parameters of oral paracetamol in frail inpatients after multiple dosing. Female sex and higher total serum bilirubin concentrations were associated with paracetamol exposure. No significant differences were observed between the tablet and granulate.

Gepubliceerd: Br J Clin Pharmacol. 2022;88(3):1020-30.
Impact factor: 3.716; Q2

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4. Non-cardiovascular medication and readmission for heart failure: an observational cohort study
Kruik-Kollöffel WJ, Vallejo-Yagüe E, Movig KLL, Linssen GCM, Heintjes EM, van der Palen J.

Background: Among heart failure (HF) patients, hospital readmissions are a major concern. The medication taken by a patient may provide information on comorbidities and conditions and may be used as an indicator to identify populations at an increased risk of HF readmission.
Aim: This study explored the use of non-cardiovascular medication at hospital discharge from the first HF admission in search of indicators of high risk of readmission for HF.
Method: The study included 22,476 HF patients from the Dutch PHARMO Database Network at their first HF hospitalization. The data was divided into training and validation sets. A Cox regression model with demographics, date of first HF hospital admission and non-cardiovascular medication present at discharge, adjusted for cardiovascular medication, was developed in the training set and subsequently implemented in the validation set.
Results: The study included 22,476 patients, mean age 76.7 years (range 18-104) and median follow-up time 2.5 years (range 0-15.7 years). During the study period 6,725 (29.9%) patients were

readmitted for HF, with a median time-to-readmission of 7 months (range 0-14.3 years). Non-cardiovascular medication associated with a high risk of readmission for HF were identified as indicators of high risk, with no implied causal relationship. Patients prescribed antigout medications presented a 25% increased risk of readmission (HR 1.25, 95%CI 1.09-1.45, P = 0.002). Patients using insulin had an 18% higher risk of readmission versus patients not using insulin (HR 1.18, 95%CI 1.06-1.32, P = 0.002), but not versus patients treated with other blood-glucose-lowering drugs. No association between the risk of readmission and NSAIDs use was observed.
Conclusion: The results suggest that diabetes is responsible for the higher HF-readmission risk observed in patients prescribed insulin. The observed risk in users of antigout medication should be further investigated. The absence of an association with the use of NSAIDs should be interpreted with caution.

Gepubliceerd: Int J Clin Pharm. 2022;44(3):762-8.
Impact factor: 2.305 ; Q4

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5. Corrigendum to "Mass spectrometry for therapeutic drug monitoring of anti-tuberculosis drugs"
Kuhlin J, Sturkenboom MGG, Ghimire S, Margineanu I, van den Elsen SHJ, Simbar N, Akkerman OW, Jongedijk EM, Koster RA, Bruchfeld J, Touw DJ, Alffenaar JC.

[This corrects the article DOI: 10.1016/j.clinms.2018.10.002.].

Gepubliceerd: J Mass Spectrom Adv Clin Lab. 2022;25:72.
Impact factor: 0 ; Q NVT

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6. Patient and Health Care Provider Perspectives on Potential Preventability of Hospital Admission for Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Qualitative Study
Leenders A, Sportel E, Poppink E, van Beurden W, van der Valk P, Brusse-Keizer M.

Purpose: Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic disease partly characterised by the occurrence of acute exacerbations (AECOPD). The need for hospital admissions for COPD exacerbations could theoretically be decreased through timely and appropriate outpatient care or self-management. The aim of this study is to explore and compare patients' and health care providers' (HCP) perspectives on the potential preventability of COPD hospitalisations and to identify strategies to prevent unnecessary hospitalisations.
Patients and Methods: Semi-structured interviews were conducted with patients admitted for an AECOPD (N = 11), HCPs on the respiratory ward (N = 11), and treating pulmonologists (N = 10). Interviews were transcribed verbatim and analysed using thematic content analysis**.**
Results: Patient and HCP perspectives on the potential preventability of hospital admissions for AECOPD often conflict. The kappa coefficients were -0.18 [95% CI: -0.46-0.11] for patients and pulmonologists and -0.28 [95% CI: -0.80-0.21] for patients and HCPs, which indicates poor agreement. The kappa coefficient for pulmonologists and HCPs was 0.14 [95% CI: -0.13-0.41], which indicates slight agreement. Patient and HCP factors that could potentially prevent hospitalisation for AECOPD were identified, including timely calling for help, recognizing and acting on symptoms, and receiving instruction about COPD, including treatment and action plans**.**
Conclusion: Patients and their HCPs have different beliefs about the potential preventability of AECOPD hospitalisations. Most patients and HCPs mentioned factors that potentially could have led to a different outcome for the current AECOPD or that could impact the patient's health status and treatment of AECOPDs in the future. The factors identified in this study indicate that shared decision

making is crucial to center the patient's perspective and individual needs and to provide timely treatment or prevention of AECOPD, thereby potentially decreasing hospital admission rates.

Gepubliceerd: Patient Prefer Adherence. 2022;16:3207-20.
Impact factor: 2.314 ; Q3

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7. Adsorption of insulin onto neonatal infusion sets: should intravenous administration of insulin to treat hyperglycemia in preterm babies on the NICU be proceeded by priming of the intravenous system, adding of albumin, or non-priming to get to a stable insulin dose?
Mian P, Bolhuis MS, Maurer JM, van Stuijvenberg M.

Insulin is used to treat neonatal hyperglycaemia when blood glucose concentrations are consistently high, and to treat neonatal diabetes. Within this brief report, a review of the existing literature is conducted to determine if intravenous administration of insulin should be proceeded by priming of the intravenous system, adding of albumin, or non-priming to get a stable insulin dose. Within this literature search, we focused on experimental insulin adsorption data (in vitro studies).

Gepubliceerd: Mol Cell Pediatr. 2022;9(1):20.
Impact factor: 0 ; Q NVT

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8. Suboptimal plasma concentrations with posaconazole suspension as prophylaxis in critically ill COVID-19 patients at risk of Covid-associated pulmonary aspergillosis
Mian P, Trof RJ, Beishuizen A, Masselink JB, Cornet AD, Sportel ET.

What is known and objective: The safety and efficacy of different antifungal agents in the prophylaxis of invasive fungal infection in patients with haematological disorders are known. We comment on the poor bioavailability of posaconazole suspension to suggest that it is not useful in critically ill COVID patients.
Comment: The increased mortality and high incidence of COVID-associated pulmonary aspergillosis (CAPA) might justify administration of off-label posaconazole for preventing CAPA, being the only drug officially registered for prophylaxis of fungal infections. We decided to initiate off-label posaconazole prophylaxis in COVID-19 patients, who were mechanically ventilated and exposed to high-dose steroids for progressive pulmonary disease or ARDS. We found that posaconazole suspension was inadequate. Very low trough levels were observed after administration, and the dose adjustments necessary for the therapeutic drug monitoring (TDM) of the drug in our critically ill ICU patients were not useful.
What is new and conclusion: Posaconazole suspension should not be used to prevent CAPA in COVID-19 patients on high-dose steroid therapy.

Gepubliceerd: J Clin Pharm Ther. 2022;47(3):383-5.
Impact factor: 2.145 ; Q4

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9. The Effect of a Structured Medication Review on Quality of Life in Parkinson's Disease
Oonk NGM, Movig KLL, van der Palen J, Nibourg SAF, Koehorst-Ter Huurne K, Nijmeijer HW, van Kesteren ME, Dorresteijn LDA.

Background: Drug therapy is important for controlling symptoms in Parkinson's disease (PD). However, it often results in complex medication regimens and could easily lead to drug related

problems (DRP), suboptimal adherence and reduced treatment efficacy. A structured medication review (SMR) could address these issues and optimize therapy, although little is known about clinical effects in PD patients.
Objective: To analyze whether an SMR improves quality of life (QoL) in PD**.**
Methods: In this multicenter randomized controlled trial, half of the 202 PD patients with polypharmacy received a community pharmacist-led SMR. The control group received usual care. Assessments at baseline, and after three and six months comprised six validated questionnaires. Primary outcome was PD specific QoL [(PDQ-39; range 0 (best QoL) - 100 (worst QoL)]. Secondary outcomes were disability score, non-motor symptoms, general health status, and personal care giver's QoL. Furthermore, DRPs, proposed interventions, and implemented modifications in medication schedules were analyzed**.**
Results: No improvement in QoL was seen six months after an SMR, with a non-significant treatment effect difference of 2.09 (-0.63;4.80) in favor of the control group. No differences were found in secondary outcomes. In total, 260 potential DRPs were identified (2.6 (±1.8) per patient), of which 62% led to drug therapy optimization**.**
Conclusion: In the current setting, a community pharmacist-led SMR did not improve QoL in PD patients, nor improved other pre-specified outcomes.

Gepubliceerd: J Parkinsons Dis. 2022;12(4):1295-306.
Impact factor: 5.520 ; Q2

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10. Pharmacokinetics of the most commonly used antihypertensive drugs throughout pregnancy methyldopa, labetalol, and nifedipine: a systematic review
van de Vusse D, Mian P, Schoenmakers S, Flint RB, Visser W, Allegaert K, Versmissen J.

Purpose: Antihypertensive drugs are among the most prescribed drugs during pregnancy. Methyldopa, labetalol, and nifedipine have been perceived safe to use during pregnancy and are therefore recommended in international guidelines for treatment of hypertension. In this review, we provide a complete overview of what is known on the pharmacokinetics (PK) of the antihypertensive drugs methyldopa, labetalol, and nifedipine throughout pregnancy**.**
Methods: A systematic search was performed to retrieve studies on the PK of methyldopa, labetalol, and nifedipine used throughout pregnancy. The search was restricted to English and original studies. The systematic search was conducted on July 27, 2021, in Embase, Medline Ovid, Web of Science, Cochrane Library, and Google Scholar. Keywords were methyldopa, labetalol, nifedipine, pharmacokinetics, pregnancy, and placenta**.**
Results: A total of 1459 unique references were identified of which title and abstract were screened. Based on this screening, 67 full-text papers were assessed, to retain 30 PK studies of which 2 described methyldopa, 12 labetalol, and 16 nifedipine. No fetal accumulation is found for any of the antihypertensive drugs studied**.**
Conclusion: We conclude that despite decades of prescribing methyldopa, labetalol, and nifedipine throughout pregnancy, descriptions of their PK during pregnancy are hampered by a large heterogeneity in the low number of available studies. Aiming for evidence-based and personalized dosing of antihypertensive medication in the future, further studies on the relationship of both PK and pharmacodynamics (including the optimal blood pressure targeting) during pregnancy and pregnancy-related pathology are urgently needed to prevent undertreatment, overtreatment, and side effects.

Gepubliceerd: Eur J Clin Pharmacol. 2022;78(11):1763-76.
Impact factor: 3.064 ; Q3

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11. Highly Variable Paracetamol Pharmacokinetics After Multiple Oral Dosing in Frail Older People: A Population Pharmacokinetic Analysis
van der Heijden LT, Mian P, Hias J, de Winter BCM, Tournoy J, Van der Linden L, Tibboel D, Walgraeve K, Flamaing J, Koch BCP, Allegaert K, Spriet I.

Introduction: Paracetamol pharmacokinetics (PK) is highly variable in older fit adults after intravenous administration. Frailty and oral administration likely result in additional variability. The aim was to determine oral paracetamol PK and variability in geriatric inpatients**.**
Methods: A population PK analysis, using NONMEM 7.2, was performed on 245 paracetamol samples in 40 geriatric inpatients (median age 87 [range 80-95] years, bodyweight 66.4 [49.3-110] kg, 92.5% frail [Edmonton Frail Scale]). All subjects received paracetamol 1000 mg as tablet (72.5%) or granulate (27.5%) three times daily. Simulations of dosing regimens (1000 mg every 6 hours [q6h] or q8h) were performed to determine target attainment, using mean steady-state concentration (C(ss-mean)) of 10 mg/L as target**.**
Results: A one-compartment model with first order absorption and lag time best described the data. The inter-individual variability was high, with absorption rate constant containing the highest variability. The inter-individual variability could not be explained by covariates. Simulations of 1000 mg q6h and q8h resulted in a C(ss-mean) of 10.8 [25-75th percentiles 8.2-12.7] and 8.13 [6.3-9.6] mg/L, respectively, for the average geriatric inpatient. The majority of the population remained off-target (22.2% [q6h] and 52.2% [q8h] <8 mg/L; 31.3 [q6h] and 7.6% [q8h] >12 mg/L)**.**
Conclusion: A population of average geriatric inpatients achieved target C(ss-mean) with paracetamol 1000 mg q6h, while q8h resulted in underexposure for the majority of them. Due to high unexplained variability, a relevant proportion remained either above or below the target concentration of 10 mg/L. Research focusing on PK, efficacy and safety is needed to recommend dosing regimens.

Gepubliceerd: Drugs Aging. 2022;39(1):83-95.
Impact factor: 4.271; Q2

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12. The Effect of Pregnancy and Inflammatory Bowel Disease on the Pharmacokinetics of Drugs Related to Inflammatory Bowel Disease-A Systematic Literature Review
Wiersma TK, Visschedijk MC, de Boer NK, Lub-de Hooge MN, Prins JR, Touw DJ, Mian P.

Due to ethical and practical reasons, a knowledge gap exists on the pharmacokinetics (PK) of inflammatory bowel disease (IBD)-related drugs in pregnant women with IBD. Before evidence-based dosing can be proposed, insight into the PK has to be gained to optimize drug therapy for both mother and fetus. This systematic review aimed to describe the effect of pregnancy and IBD on the PK of drugs used for IBD. One aminosalicylate study, two thiopurine studies and twelve studies with biologicals were included. Most drugs within these groups presented data over multiple moments before, during and after pregnancy, except for mesalazine, ustekinumab and golimumab. The studies for mesalazine, ustekinumab and golimumab did not provide enough data to demonstrate an effect of pregnancy on concentration and PK parameters. Therefore, no evidence-based dosing advice was given. The 6-thioguanine nucleotide levels decreased during pregnancy to 61% compared to pre-pregnancy levels. The potentially toxic metabolite 6-methylmercaptopurine (6-MMP) increased to maximal 209% of the pre-pregnancy levels. Although the PK of the thiopurines changed throughout pregnancy, no evidence-based dosing advice was provided. One study suggested that caution should be exercised when the thiopurine dose is adjusted, due to shunting 6-MMP levels. For the biologicals, infliximab levels increased, adalimumab stayed relatively stable and vedolizumab levels tended to decrease during pregnancy. Although the PK of the biologicals changed throughout

pregnancy, no evidence-based dosing advice for biologicals was provided. Other drugs retrieved from the literature search were mesalazine, ustekinumab and golimumab. We conclude that limited studies have been performed on PK parameters during pregnancy for drugs used in IBD. Therefore, more extensive research to determine the values of PK parameters is warranted. After gathering the PK data, evidence-based dosing regimens can be developed.

Gepubliceerd: Pharmaceutics. 2022;14(6).
Impact factor: 6.525 ; Q1

Totale impact factor: 89.281
Gemiddelde impact factor: 7.440

Aantal artikelen 1e, 2e of laatste auteur: 8
Totale impact factor: 78.272
Gemiddelde impact factor: 9.784

Klinische fysica

1. Assessing the Microcirculation of the Foot with Laser Speckle Contrast Imaging During Endovascular and Hybrid Revascularisation Procedures in Patients with Chronic Limb Threatening Ischaemia
Wermelink B, Mennes OA, Van Baal JG, Steenbergen W, Geelkerken RH, Study group includes: Aarnink SH; Beuk R; Brusse-Keiser M; Haalboom M; Meerwaldt R; Willigendael EM.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2022;63(6):898-9.
Impact factor: 6.427 ; Q1

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2. Cone-beam computed tomography-guided online adaptive radiotherapy is feasible for prostate cancer patients
Zwart LGM, Ong F, Ten Asbroek LA, van Dieren EB, Koch SA, Bhawanie A, de Wit E, Dasselaar JJ.

Background and Purpose: Studies have shown the potential of cone-beam computed tomography (CBCT)-guided online adaptive radiotherapy (oART) for prostate cancer patients in a simulation environment. The aim of this study was to evaluate the feasibility of the clinical implementation of CBCT-guided oART for prostate cancer patients.
Material and Methods: Between February and July 2020, eleven prostate cancer patients were treated with CBCT-guided oART using a fractionation scheme of 20 × 3 Gy to the prostate and 20 × 2.7/3.0 Gy to the seminal vesicles for more advanced stages. The on-couch adaptive workflow consisted of influencer (prostate, seminal vesicles, rectum, bladder) review, target review, scheduled (re-calculated) and adapted (re-optimized) plan generation, an independent QA procedure and treatment delivery. Treatment time, proportion of adapted fractions and reasons for plan adaptation were evaluated**.**
Results: Mean total treatment time (±SD) from CBCT acquisition to end of treatment delivery was 17.5 ± 3.2 min (range: 10.8-28.8 min). In all 220 fractions, the PTV coverage was increased for the adapted plan compared to the scheduled plan. The V60Gy of bladder and rectum were below the constraints (<5% and <3%) for both scheduled and adapted plans in 171 out of 220 fractions and for the adapted plan only in 30 out of 220 fractions. In 19 out of 220 fractions, the V60Gy of the bladder and/or rectum was above the constraint for the adapted plan.
Conclusions: The clinical implementation of CBCT-guided oART is feasible for prostate cancer patients. The adaptive workflow is possible within twenty minutes on average with a dedicated team.

Gepubliceerd: Phys Imaging Radiat Oncol. 2022;22:98-103.
Impact factor: 3.700 ; Q NVT

Totale impact factor: 10.127
Gemiddelde impact factor: 5.064

Aantal artikelen 1e, 2e of laatste auteur: 0
Totale impact factor: 0
Gemiddelde impact factor: 0

Klinische psychologie

1. Impaired Visual Emotion Recognition After Minor Ischemic Stroke
Smith-Spijkerboer W, Meeske K, van der Palen JAM, den Hertog HM, Smeets-Schouten AS, van Hout M, Dorresteijn LDA.

Objective: To assess the prevalence of impaired visual emotion recognition in patients who have experienced a minor ischemic stroke in the subacute phase and to determine associated factors of impaired visual emotion recognition.
Design:A prospective observational study. SETTING: Stroke unit of a teaching hospital. PARTICIPANTS: Patients with minor ischemic stroke (N=112)**.**
Interventions: Not applicable. MAIN OUTCOME MEASURES: Patients with minor stroke underwent a neuropsychological assessment in the subacute phase for visual emotion recognition by the Ekman 60 Faces Test and for general cognition. Univariable linear regression analyses were performed to identify associated factors of emotion recognition impairment**.**
Results: In 112 minor stroke patients, we found a prevalence of 25% of impaired visual emotion recognition. This was significantly correlated with impaired general cognition. Nevertheless, 10.9% of patients with normal general cognition still had impaired emotion recognition. Mood was negatively associated. Stroke localization, hemisphere side, and sex were not associated**.**
Conclusion: Impaired visual emotion recognition is found in about one-quarter of patients with minor ischemic stroke.

Gepubliceerd: Arch Phys Med Rehabil. 2022;103(5):958-63.
Impact factor: 4.060 ; Q1

Totale impact factor: 4.060
Gemiddelde impact factor: 4.060

Aantal artikelen 1e, 2e of laatste auteur: 0
Totale impact factor: 0
Gemiddelde impact factor: 0

KNO

1. A Comprehensive Grading System for a Magnetic Sentinel Lymph Node Biopsy Procedure in Head and Neck Cancer Patients
Nieuwenhuis ER, Kolenaar B, Hof JJ, van Baarlen J, van Bemmel AJM, Christenhusz A, Scheenen TWJ, Ten Haken B, de Bree R, Alic L.

A magnetic sentinel lymph node biopsy ((SLN)B) procedure has recently been shown feasible in oral cancer patients. However, a grading system is absent for proper identification and classification, and thus for clinical reporting. Based on data from eight complete magnetic SLNB procedures, we propose a provisional grading system. This grading system includes: (1) a qualitative five-point grading scale for MRI evaluation to describe iron uptake by LNs; (2) an ex vivo count of resected SLN with a magnetic probe to quantify iron amount; and (3) a qualitative five-point grading scale for histopathologic examination of excised magnetic SLNs. Most SLNs with iron uptake were identified and detected in level II. In this level, most variance in grading was seen for MRI and histopathology; MRI and medullar sinus were especially highly graded, and cortical sinus was mainly low graded. On average 82 ± 58 µg iron accumulated in harvested SLNs, and there were no significant differences in injected tracer dose (22.4 mg or 11.2 mg iron). In conclusion, a first step was taken in defining a comprehensive grading system to gain more insight into the lymphatic draining system during a magnetic SLNB procedure.

Gepubliceerd: Cancers (Basel). 2022;14(3).
Impact factor: 6.575; Q1

Totale impact factor: 6.575
Gemiddelde impact factor: 6.575

Aantal artikelen 1e, 2e of laatste auteur: 0
Totale impact factor: 0
Gemiddelde impact factor: 0

Longgeneeskunde

1. Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With High Risk for Postoperative Complications: Results of a Randomized Clinical Trial
Berkel AEM, Bongers BC, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, Wymenga M, Bigirwamungu-Bargeman M, van der Palen J, van Det MJ, van Meeteren NLU, Klaase JM.

Objective: To assess the effects of a 3-week community-based exercise program on 30-day postoperative complications in high-risk patients scheduled for elective colorectal resection for (pre)malignancy.
Summary Background data: Patients with a low preoperative aerobic fitness undergoing colorectal surgery have an increased risk of postoperative complications. It remains, however, to be demonstrated whether prehabilitation in these patients reduces postoperative complications**.**
Methods: This 2-center, prospective, single-blinded randomized clinical trial was carried out in 2 large teaching hospitals in the Netherlands. Patients (≥60 years) with colorectal (pre)malignancy scheduled for elective colorectal resection and with a score ≤7 metabolic equivalents on the veterans-specific activity questionnaire were randomly assigned to the prehabilitation group or the usual care group by using block-stratified randomization. An oxygen uptake at the ventilatory anaerobic threshold <11 mL/kg/min at the baseline cardiopulmonary exercise test was the final inclusion criterion. Inclusion was based on a power analysis. Patients in the prehabilitation group participated in a personalized 3-week (3 sessions per week, nine sessions in total) supervised exercise program given in community physical therapy practices before colorectal resection. Patients in the reference group received usual care. The primary outcome was the number of patients with one or more complications within 30 days of surgery, graded according to the Clavien-Dindo classification. Data were analyzed on an intention-to-treat basis**.**
Results: Between February 2014 and December 2018, 57 patients [30 males and 27 females; mean age 73.6 years (standard deviation 6.1), range 61-88 years] were randomized to either prehabilitation (n = 28) or usual care (n = 29). The rate of postoperative complications was lower in the prehabilitation group (n = 12, 42.9%) than in the usual care group (n = 21, 72.4%, relative risk 0.59, 95% confidence interval 0.37-0.96, P = 0.024).
Conclusions: Exercise prehabilitation reduced postoperative complications in high-risk patients scheduled to undergo elective colon resection for (pre)malignancy. Prehabilitation should be considered as usual care in high-risk patients scheduled for elective colon, and probably also rectal, surgery.

Gepubliceerd: Ann Surg. 2022;275(2):e299-e306.
Impact factor: 13.787 ; Q1

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2. Difference in survival between COPD patients with an impaired immune reaction versus an adequate immune reaction to seasonal influenza vaccination: The COMIC study
Brusse-Keizer M, Citgez E, Zuur-Telgen M, Kerstjens HAM, Rijkers G, Van der Valk PDLPM, van der Palen J.

Aim: To study the hypothesis that COPD patients who do not achieve seroprotective levels after influenza vaccination, are a less immune-competent group with a higher risk of morbidity and mortality**.**
Methods: 578 patients included in the COMIC cohort had pre- and post-vaccination stable state blood samples in which influenza-vaccine specific antibodies were measured. Post-vaccination titers of ≥40 were considered protective and indicative of being immuno-competent. Primary outcome was

all-cause mortality. Morbidity was defined as time till first severe acute exacerbation in COPD (severe AECOPD) and time till first community acquired pneumonia (CAP)**.**
Results: 42% of the patients achieved seroprotective levels to both H1N1 and H3N2 after vaccination. Seroprotective levels to H3N2 were markedly higher (96%) than to H1N1(43%). Having seroprotective levels to both H1N1 and H3N2 was not associated with less morbidity (severe AECOPD HR 0.91 (95% 0.66-1.25; p = 0.564) (CAP HR 1.23 (95% 0.75-2.00; p = 0.412)) or lower mortality (HR 1.10(95% 0.87-1.38; p = 0.433))**.**
Conclusion: In a large well-characterized COPD cohort only the minority of patients achieved seroprotective titers to H1N1 and H3N1 after the yearly influenza vaccination. While achieving seroprotection after vaccination can be considered a surrogate marker of being immunocompetent, this was not associated with lower morbidity and mortality. Whether this means that the immune status is not a relevant pheno/endotype in COPD patients for the course of their disease or that seroprotection is not an adequate (surrogate) marker to define the immune status in COPD needs to be further studied.

Gepubliceerd: Respir Med. 2022;197:106851.
Impact factor: 4.582 ; Q2

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3. Life-prolonging treatment restrictions and outcomes in patients with cancer and COVID-19: an update from the Dutch Oncology COVID-19 Consortium
de Joode K, Tol J, Hamberg P, Cloos M, Kastelijn EA, Borgers JSW, Nuij V, Klaver Y, Herder GJM, Mutsaers P, Dumoulin DW, Oomen-de Hoop E, van Diemen NGJ, Libourel EJ, Geraedts EJ, Bootsma GP, van der Leest CH, Peerdeman AL, Herbschleb KH, Visser OJ, Bloemendal HJ, van Laarhoven HWM, de Vries EGE, Hendriks LEL, Beerepoot LV, Westgeest HM, van den Berkmortel F, Haanen J, Dingemans AC, van der Veldt AAM, DOCC investigators; Citgez E.

Aim of the study: The coronavirus disease 2019 (COVID-19) pandemic significantly impacted cancer care. In this study, clinical patient characteristics related to COVID-19 outcomes and advanced care planning, in terms of non-oncological treatment restrictions (e.g. do-not-resuscitate codes), were studied in patients with cancer and COVID-19**.**
Methods: The Dutch Oncology COVID-19 Consortium registry was launched in March 2020 in 45 hospitals in the Netherlands, primarily to identify risk factors of a severe COVID-19 outcome in patients with cancer. Here, an updated analysis of the registry was performed, and treatment restrictions (e.g. do-not-intubate codes) were studied in relation to COVID-19 outcomes in patients with cancer. Oncological treatment restrictions were not taken into account**.**
Results: Between 27th March 2020 and 4th February 2021, 1360 patients with cancer and COVID-19 were registered. Follow-up data of 830 patients could be validated for this analysis. Overall, 230 of 830 (27.7%) patients died of COVID-19, and 60% of the remaining 600 patients with resolved COVID-19 were admitted to the hospital. Patients with haematological malignancies or lung cancer had a higher risk of a fatal outcome than other solid tumours. No correlation between anticancer therapies and the risk of a fatal COVID-19 outcome was found. In terms of end-of-life communication, 50% of all patients had restrictions regarding life-prolonging treatment (e.g. do-not-intubate codes). Most identified patients with treatment restrictions had risk factors associated with fatal COVID-19 outcome**.**
Conclusion: There was no evidence of a negative impact of anticancer therapies on COVID-19 outcomes. Timely end-of-life communication as part of advanced care planning could save patients from prolonged suffering and decrease burden in intensive care units. Early discussion of treatment restrictions should therefore be part of routine oncological care, especially during the COVID-19 pandemic.

Gepubliceerd: Eur J Cancer. 2022;160:261-72.
Impact factor: 10.002 ; Q1

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4. ISARIC-COVID-19 dataset: A Prospective, Standardized, Global Dataset of Patients Hospitalized with COVID-19
Garcia-Gallo E, Merson L, Kennon K, Kelly S, Citarella BW, Fryer DV, Shrapnel S, Lee J, Duque S, Fuentes YV, Balan V, Smith S, Wei J, Gonçalves BP, Russell CD, Sigfrid L, Dagens A, Olliaro PL, Baruch J, Kartsonaki C, Dunning J, Rojek A, Rashan A, Beane A, Murthy S, Reyes LF, ISARIC Clinical Characterization Group: Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, van Veen H, Vonkeman H.

The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) COVID-19 dataset is one of the largest international databases of prospectively collected clinical data on people hospitalized with COVID-19. This dataset was compiled during the COVID-19 pandemic by a network of hospitals that collect data using the ISARIC-World Health Organization Clinical Characterization Protocol and data tools. The database includes data from more than 705,000 patients, collected in more than 60 countries and 1,500 centres worldwide. Patient data are available from acute hospital admissions with COVID-19 and outpatient follow-ups. The data include signs and symptoms, pre-existing comorbidities, vital signs, chronic and acute treatments, complications, dates of hospitalization and discharge, mortality, viral strains, vaccination status, and other data. Here, we present the dataset characteristics, explain its architecture and how to gain access, and provide tools to facilitate its use.

Gepubliceerd: Sci Data. 2022;9(1):454.
Impact factor: 8.501 ; Q1

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5. Allergen provocation tests in respiratory research: building on 50 years of experience
Gauvreau GM, Davis BE, Scadding G, Boulet LP, Bjermer L, Chaker A, Cockcroft DW, Dahlén B, Fokkens W, Hellings P, Lazarinis N, O'Byrne PM, Tufvesson E, Quirce S, Van Maaren M, de Jongh FH, Diamant Z.

The allergen provocation test is an established model of allergic airway diseases, including asthma and allergic rhinitis, allowing the study of allergen-induced changes in respiratory physiology and inflammatory mechanisms in sensitised individuals as well as their associations. In the upper airways, allergen challenge is focused on the clinical and pathophysiological sequelae of the early allergic response, and is applied both as a diagnostic tool and in research settings. In contrast, bronchial allergen challenge has almost exclusively served as a research tool in specialised research settings with a focus on the late asthmatic response and the underlying type 2 inflammation. The allergen-induced late asthmatic response is also characterised by prolonged airway narrowing, increased nonspecific airway hyperresponsiveness and features of airway remodelling including the small airways, and hence allows the study of several key mechanisms and features of asthma. In line with these characteristics, allergen challenge has served as a valued tool to study the cross-talk of the upper and lower airways and in proof-of-mechanism studies of drug development. In recent years, several new insights into respiratory phenotypes and endotypes including the involvement of the upper and small airways, innovative biomarker sampling methods and detection techniques, refined lung function testing as well as targeted treatment options further shaped the applicability of the allergen provocation test in precision medicine. These topics, along with descriptions of subject populations and safety, in line with the updated Global Initiative for Asthma 2021 document, will be addressed in this review.

Gepubliceerd: Eur Respir J. 2022;60(2).
Impact factor: 33.801 ; Q1

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6. Stepwise model development and simultaneous validation to keep up with clinically relevant and rapidly changing diagnostic techniques
Haalboom M, Kort S, van der Palen J.

Gepubliceerd: J Clin Epidemiol. 2022;142:332.
Impact factor: 7.407 ; Q1

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7. Using a stepwise approach to simultaneously develop and validate machine learning based prediction models
Haalboom M, Kort S, van der Palen J.

Accurate diagnosis of a disease is essential in healthcare. Prediction models, based on classical regression techniques, are widely used in clinical practice. Machine Learning (ML) techniques might be preferred in case of a large amount of data per patient and relatively limited numbers of subjects. However, this increases the risk of overfitting, and external validation is imperative. However, in the field of ML, new and more efficient techniques are developed rapidly, and if recruiting patients for a validation study is time consuming, the ML technique used to develop the first model might have been surpassed by more efficient ML techniques, rendering this original model no longer relevant. We demonstrate a stepwise design for simultaneous development and validation of prediction models based on ML techniques. The design enables - in one study - evaluation of the stability and robustness of a prediction model over increasing sample size as well as assessment of the stability of sensitivity/specificity at a chosen cut-off. This will shorten the time to introduction of a new test in health care. We finally describe how to use regular clinical parameters in conjunction with ML based predictions, to further enhance differentiation between subjects with and without a disease.

Gepubliceerd: J Clin Epidemiol. 2022;142:305-10.
Impact factor: 7.407 ; Q1

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8. Real-World Effectiveness of Reslizumab in Patients With Severe Eosinophilic Asthma - First Initiators and Switchers
Hashimoto S, Kroes JA, Eger KA, Mau Asam PF, Hofstee HB, Bendien SA, Braunstahl GJ, Broeders M, Imming LM, Langeveld B, Maitland-van der Zee AH, Oud KTM, Patberg KW, Smeenk F, Romme E, van Bezouw MJ, van de Ven MJ, van Veen A, van Velzen E, van Veen I, Weersink EJM, Ten Brinke A, Sont JK, Bel EH.

Background: Reslizumab, a biologic targeting IL-5, has been shown to reduce asthma exacerbations and maintenance oral corticosteroid use in randomized controlled trials and pre-post studies in patients with severe eosinophilic asthma. However, real-world effectiveness data of reslizumab are scarce, and it is unknown whether reslizumab has added value after switching from another type 2 biologic.
Objective: To evaluate (1) the real-world effectiveness of reslizumab on severe asthma exacerbations, maintenance oral corticosteroid use, and overall treatment response, both in biologic-naive patients who initiated reslizumab and in those who switched from another type 2 biologic; and (2) physicians' experience with reslizumab treatment**.**

Methods: This observational real-world study evaluated data from 134 adults with severe eosinophilic asthma included in the Dutch severe asthma registry (RAPSODI), who initiated reslizumab treatment (4-weekly infusions, 0.3 mg/kg) before April 2020 and had follow-up data for 6 months and greater. Clinical asthma experts completed surveys on their experience with reslizumab treatment**.**
Results: Overall, reslizumab reduced the exacerbation rate (odds ratio [95% CI] = 0.10 [0.05-0.21]; P < .001), oral corticosteroid use (OR [95% CI], 0.2 [0.0-0.5]; P < .001), and maintenance dose (median [CI], 5.0 [0.0-10.0] to 0.0 [0.0-5.0]; P < .001), with comparable results in biologic-naive reslizumab initiators and switchers. The overall response to reslizumab was graded good or excellent in 59.2% of patients. The additive effectiveness of reslizumab after switching from another biologic was reflected in physicians' surveys.
Conclusions: Real-world data show that reslizumab reduces severe asthma exacerbations and oral corticosteroid use in patients with severe eosinophilic asthma, both in biologic-naive reslizumab initiators and in those who switched from another type 2 biologic. This additional value of reslizumab was recognized by clinical asthma experts.

Gepubliceerd: J Allergy Clin Immunol Pract. 2022;10(8):2099-108.e6.
Impact factor: 11.022 ; Q1

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9. Clinical presentation, disease course, and outcome of COVID-19 in hospitalized patients with and without pre-existing cardiac disease: a cohort study across 18 countries
CAPACITY-COVID Collaborative Consortium and LEOSS Study Group; Delsing CE, Meijs MFL, van Veen H, Vonkeman HE.

Aims: Patients with cardiac disease are considered high risk for poor outcomes following hospitalization with COVID-19. The primary aim of this study was to evaluate heterogeneity in associations between various heart disease subtypes and in-hospital mortality**.**
Methods and Results: We used data from the CAPACITY-COVID registry and LEOSS study. Multivariable Poisson regression models were fitted to assess the association between different types of pre-existing heart disease and in-hospital mortality. A total of 16 511 patients with COVID-19 were included (21.1% aged 66-75 years; 40.2% female) and 31.5% had a history of heart disease. Patients with heart disease were older, predominantly male, and often had other comorbid conditions when compared with those without. Mortality was higher in patients with cardiac disease (29.7%; n = 1545 vs. 15.9%; n = 1797). However, following multivariable adjustment, this difference was not significant [adjusted risk ratio (aRR) 1.08, 95% confidence interval (CI) 1.02-1.15; P = 0.12 (corrected for multiple testing)]. Associations with in-hospital mortality by heart disease subtypes differed considerably, with the strongest association for heart failure (aRR 1.19, 95% CI 1.10-1.30; P < 0.018) particularly for severe (New York Heart Association class III/IV) heart failure (aRR 1.41, 95% CI 1.20-1.64; P < 0.018). None of the other heart disease subtypes, including ischaemic heart disease, remained significant after multivariable adjustment. Serious cardiac complications were diagnosed in <1% of patients**.**
Conclusion: Considerable heterogeneity exists in the strength of association between heart disease subtypes and in-hospital mortality. Of all patients with heart disease, those with heart failure are at greatest risk of death when hospitalized with COVID-19. Serious cardiac complications are rare during hospitalization.

Gepubliceerd: Eur Heart J. 2022;43(11):1104-20.
Impact factor: 35.855 ; Q1

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10. Home Treatment Compared to Initial Hospitalization in Normotensive Patients with Acute Pulmonary Embolism in the Netherlands: A Cost Analysis
Hendriks SV, van den Hout WB, van Bemmel T, Bistervels IM, Eijsvogel M, Faber LM, Hofstee HMA, van der Hulle T, Iglesias Del Sol A, Kruip M, Mairuhu ATA, Middeldorp S, Nijkeuter M, Huisman MV, Klok FA.

Background: Venous thromboembolism constitutes substantial health care costs amounting to approximately 60 million euros per year in the Netherlands. Compared with initial hospitalization, home treatment of pulmonary embolism (PE) is associated with a cost reduction. An accurate estimation of cost savings per patient treated at home is currently lacking.
Aim: The aim of this study was to compare health care utilization and costs during the first 3 months after a PE diagnosis in patients who are treated at home versus those who are initially hospitalized**.**
Methods: Patient-level data of the YEARS cohort study, including 383 normotensive patients diagnosed with PE, were used to estimate the proportion of patients treated at home, mean hospitalization duration in those who were hospitalized, and rates of PE-related readmissions and complications. To correct for baseline differences within the two groups, regression analyses was performed. The primary outcome was the average total health care costs during a 3-month follow-up period for patients initially treated at home or in hospital**.**
Results: Mean hospitalization duration for the initial treatment was 0.69 days for those treated initially at home (n = 181) and 4.3 days for those initially treated in hospital (n = 202). Total average costs per hospitalized patient were €3,209 and €1,512 per patient treated at home. The adjusted mean difference was €1,483 (95% confidence interval: €1,181-1,784)**.**
Conclusion: Home treatment of hemodynamically stable patients with acute PE was associated with an estimated net cost reduction of €1,483 per patient. This difference underlines the advantage of triage-based home treatment of these patients.

Gepubliceerd: Thromb Haemost. 2022;122(3):427-33.
Impact factor: 16.041 ; Q1

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11. Age is the main determinant of COVID-19 related in-hospital mortality with minimal impact of pre-existing comorbidities, a retrospective cohort study
Henkens M, Raafs AG, Verdonschot JAJ, Linschoten M, van Smeden M, Wang P, van der Hooft BHM, Tieleman R, Janssen MLF, Ter Bekke RMA, Hazebroek MR, van der Horst ICC, Asselbergs FW, Magdelijns FJH, Heymans SRB, M.F.L. CAPACITY-COVID Collaborative Consortium and LEOSS Study Group; Delsing CE, Meijs MFL, van Veen H, Vonkeman HE.

Background: Age and comorbidities increase COVID-19 related in-hospital mortality risk, but the extent by which comorbidities mediate the impact of age remains unknown**.**
Methods: In this multicenter retrospective cohort study with data from 45 Dutch hospitals, 4806 proven COVID-19 patients hospitalized in Dutch hospitals (between February and July 2020) from the CAPACITY-COVID registry were included (age 69[58-77]years, 64% men). The primary outcome was defined as a combination of in-hospital mortality or discharge with palliative care. Logistic regression analysis was performed to analyze the associations between sex, age, and comorbidities with the primary outcome. The effect of comorbidities on the relation of age with the primary outcome was evaluated using mediation analysis**.**
Results: In-hospital COVID-19 related mortality occurred in 1108 (23%) patients, 836 (76%) were aged ≥70 years (70+). Both age 70+ and female sex were univariably associated with outcome (odds ratio [OR]4.68, 95%confidence interval [4.02-5.45], OR0.68[0.59-0.79], respectively;both p< 0.001). All comorbidities were univariably associated with outcome (p<0.001), and all but dyslipidemia remained significant after adjustment for age70+ and sex. The impact of comorbidities was

attenuated after age-spline adjustment, only leaving female sex, diabetes mellitus (DM), chronic kidney disease (CKD), and chronic pulmonary obstructive disease (COPD) significantly associated (female OR0.65[0.55-0.75], DM OR1.47[1.26-1.72], CKD OR1.61[1.32-1.97], COPD OR1.30[1.07-1.59]). Pre-existing comorbidities in older patients negligibly (<6% in all comorbidities) mediated the association between higher age and outcome.
Conclusions: Age is the main determinant of COVID-19 related in-hospital mortality, with negligible mediation effect of pre-existing comorbidities.
Trial registration: CAPACITY-COVID (NCT04325412).

Gepubliceerd: BMC Geriatr. 2022;22(1):184.
Impact factor: 4.070 ; Q2

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12. Intermediate-high risk pulmonary embolism: identification and treatment
Jager NM, Eijsvogel MMM, Wagenaar M, Beishuizen A, Trof RJ.

Patients with intermediate-high risk pulmonary embolism have a different mix of clinical symptoms. Optimal treatment of patients with intermediate high-risk pulmonary embolism is necessary to prevent short-term mortality. According to the current guidelines, the use of standard coagulation is the treatment of choice in hemodynamic stable patients with intermediate-high risk pulmonary embolism. Systemic thrombolytic therapy is recommended in patients with intermediate-high risk pulmonary embolism who circulatory deteriorate or who did not respond appropriately to standard anticoagulation. Catheter-guided thrombolysis is reserved for patients with intermediate-high risk pulmonary embolism who have a contraindication for systemic thrombolysis or did not respond to systemic thrombolysis. The timing and choice for the right treatment are significant treatment dilemmas. The development of pulmonary embolism response teams helps in the decision-making in patients with intermediate high-risk pulmonary embolism.

Gepubliceerd: Ned Tijdschr Geneeskd. 2022;166.
Impact factor: 0 ; Q NVT

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13. Patient and Health Care Provider Perspectives on Potential Preventability of Hospital Admission for Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Qualitative Study
Leenders A, Sportel E, Poppink E, van Beurden W, van der Valk P, Brusse-Keizer M.

Purpose: Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic disease partly characterised by the occurrence of acute exacerbations (AECOPD). The need for hospital admissions for COPD exacerbations could theoretically be decreased through timely and appropriate outpatient care or self-management. The aim of this study is to explore and compare patients' and health care providers' (HCP) perspectives on the potential preventability of COPD hospitalisations and to identify strategies to prevent unnecessary hospitalisations.
Patients and Methods: Semi-structured interviews were conducted with patients admitted for an AECOPD (N = 11), HCPs on the respiratory ward (N = 11), and treating pulmonologists (N = 10). Interviews were transcribed verbatim and analysed using thematic content analysis**.**
Results: Patient and HCP perspectives on the potential preventability of hospital admissions for AECOPD often conflict. The kappa coefficients were -0.18 [95% CI: -0.46-0.11] for patients and pulmonologists and -0.28 [95% CI: -0.80-0.21] for patients and HCPs, which indicates poor agreement. The kappa coefficient for pulmonologists and HCPs was 0.14 [95% CI: -0.13-0.41], which indicates slight agreement. Patient and HCP factors that could potentially prevent hospitalisation for

AECOPD were identified, including timely calling for help, recognizing and acting on symptoms, and receiving instruction about COPD, including treatment and action plans**.**
Conclusion: Patients and their HCPs have different beliefs about the potential preventability of AECOPD hospitalisations. Most patients and HCPs mentioned factors that potentially could have led to a different outcome for the current AECOPD or that could impact the patient's health status and treatment of AECOPDs in the future. The factors identified in this study indicate that shared decision making is crucial to center the patient's perspective and individual needs and to provide timely treatment or prevention of AECOPD, thereby potentially decreasing hospital admission rates.

Gepubliceerd: Patient Prefer Adherence. 2022;16:3207-20.
Impact factor: 2.314 ; Q3

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14. International consensus on lung function testing during the COVID-19 pandemic and beyond
McGowan A, Laveneziana P, Bayat S, Beydon N, Boros PW, Burgos F, Fležar M, Franczuk M, Galarza MA, Kendrick AH, Lombardi E, Makonga-Braaksma J, McCormack MC, Plantier L, Stanojevic S, Steenbruggen I, Thompson B, Coates AL, Wanger J, Cockcroft DW, Culver B, Sylvester K, De Jongh F.

Coronavirus disease 2019 (COVID-19) has negatively affected the delivery of respiratory diagnostic services across the world due to the potential risk of disease transmission during lung function testing. Community prevalence, reoccurrence of COVID-19 surges and the emergence of different variants of SARS-CoV-2 have impeded attempts to restore services. Finding consensus on how to deliver safe lung function services for both patients attending and for staff performing the tests are of paramount importance. This international statement presents the consensus opinion of 23 experts in the field of lung function and respiratory physiology balanced with evidence from the reviewed literature. It describes a robust roadmap for restoration and continuity of lung function testing services during the COVID-19 pandemic and beyond. Important strategies presented in this consensus statement relate to the patient journey when attending for lung function tests. We discuss appointment preparation, operational and environmental issues, testing room requirements including mitigation strategies for transmission risk, requirement for improved ventilation, maintaining physical distance and use of personal protection equipment. We also provide consensus opinion on precautions relating to specific tests, filters, management of special patient groups and alternative options to testing in hospitals. The pandemic has highlighted how vulnerable lung function services are and forces us to re-think how long-term mitigation strategies can protect our services during this and any possible future pandemic. This statement aspires to address the safety concerns that exist and provide strategies to make lung function tests and the testing environment safer when tests are required.

Gepubliceerd: ERJ Open Res. 2022;8(1).
Impact factor: 4.239 ; Q2

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15. Respiratory support in patients with severe COVID-19 in the International Severe Acute Respiratory and Emerging Infection (ISARIC) COVID-19 study: a prospective, multinational, observational study
Reyes LF, Murthy S, Garcia-Gallo E, Merson L, Ibáñez-Prada ED, Rello J, Fuentes YV, Martin-Loeches I, Bozza F, Duque S, Taccone FS, Fowler RA, Kartsonaki C, Gonçalves BP, Citarella BW, Aryal D, Burhan E, Cummings MJ, Delmas C, Diaz R, Figueiredo-Mello C, Hashmi M, Panda PK, Jiménez MP, Rincon DFB, Thomson D, Nichol A, Marshall JC, Olliaro PL, ISARIC Characterization Group: Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H..

Background: Up to 30% of hospitalised patients with COVID-19 require advanced respiratory support, including high-flow nasal cannulas (HFNC), non-invasive mechanical ventilation (NIV), or invasive mechanical ventilation (IMV). We aimed to describe the clinical characteristics, outcomes and risk factors for failing non-invasive respiratory support in patients treated with severe COVID-19 during the first two years of the pandemic in high-income countries (HICs) and low middle-income countries (LMICs)**.**
Methods: This is a multinational, multicentre, prospective cohort study embedded in the ISARIC-WHO COVID-19 Clinical Characterisation Protocol. Patients with laboratory-confirmed SARS-CoV-2 infection who required hospital admission were recruited prospectively. Patients treated with HFNC, NIV, or IMV within the first 24 h of hospital admission were included in this study. Descriptive statistics, random forest, and logistic regression analyses were used to describe clinical characteristics and compare clinical outcomes among patients treated with the different types of advanced respiratory support**.**
Results: A total of 66,565 patients were included in this study. Overall, 82.6% of patients were treated in HIC, and 40.6% were admitted to the hospital during the first pandemic wave. During the first 24 h after hospital admission, patients in HICs were more frequently treated with HFNC (48.0%), followed by NIV (38.6%) and IMV (13.4%). In contrast, patients admitted in lower- and middle-income countries (LMICs) were less frequently treated with HFNC (16.1%) and the majority received IMV (59.1%). The failure rate of non-invasive respiratory support (i.e. HFNC or NIV) was 15.5%, of which 71.2% were from HIC and 28.8% from LMIC. The variables most strongly associated with non-invasive ventilation failure, defined as progression to IMV, were high leukocyte counts at hospital admission (OR [95%CI]; 5.86 [4.83-7.10]), treatment in an LMIC (OR [95%CI]; 2.04 [1.97-2.11]), and tachypnoea at hospital admission (OR [95%CI]; 1.16 [1.14-1.18]). Patients who failed HFNC/NIV had a higher 28-day fatality ratio (OR [95%CI]; 1.27 [1.25-1.30]).
Conclusions: In the present international cohort, the most frequently used advanced respiratory support was the HFNC. However, IMV was used more often in LMIC. Higher leucocyte count, tachypnoea, and treatment in LMIC were risk factors for HFNC/NIV failure. HFNC/NIV failure was related to worse clinical outcomes, such as 28-day mortality. Trial registration This is a prospective observational study; therefore, no health care interventions were applied to participants, and trial registration is not applicable.

Gepubliceerd: Crit Care. 2022;26(1):276.
Impact factor: 19.344; Q1

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16. Simultaneous measurement of diaphragm activity, chest impedance, and ECG using three standard cardiorespiratory monitoring electrodes
Scholten AWJ, van Leuteren RW, de Jongh FH, van Kaam AH, Hutten GJ.

Introduction: Current cardiorespiratory monitoring in neonates with electrocardiogram (ECG) and chest impedance (CI) has limitations. Adding transcutaneous electromyography of the diaphragm (dEMG) may improve respiratory monitoring, but requires additional hardware. We aimed to determine the feasibility of measuring dEMG and ECG/CI simultaneously using the standard ECG/CI hardware, with its three electrodes repositioned to dEMG electrode locations**.**
Methods: Thirty infants (median postmenstrual age 30.4 weeks) were included. First, we assessed the feasibility of extracting dEMG from the ECG-signal. If successful, the agreement between dEMG-based respiratory rate (RR), using three different ECG-leads, and a respiratory reference signal was assessed using the Bland-Altman analysis and the intraclass correlation coefficient (ICC). Furthermore, we studied the agreement between CI-based RR and the reference signal with the electrodes placed at the standard and dEMG position. Finally, we explored the quality of the ECG-signal at the different electrode positions**.**

Results: In 15 infants, feasibility of measuring dEMG with the monitoring electrodes was confirmed. In the next 15 infants, comparing dEMG-based RR to the reference signal resulted in a mean difference and limits of agreement for ECG-lead I, II and III of 4.2 [-8.2 to 16.6], 4.3 [-10.7 to 19.3] and 5.0 [-14.2 to 24.2] breaths/min, respectively. ICC analysis showed a moderate agreement for all ECG-leads. CI-based RR agreement was similar at the standard and dEMG electrode position. An exploratory analysis suggested similar quality of the ECG-signal at both electrode positions**.**
Conclusion: Measuring dEMG using the ECG/CI hardware with its electrodes on the diaphragm is feasible, leaving ECG/CI monitoring unaffected.

Gepubliceerd: Pediatr Pulmonol. 2022;57(11):2754-62.
Impact factor: 4.090 ; Q1

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17. Feasibility of wireless cardiorespiratory monitoring with dry electrodes incorporated in a belt in preterm infants
Scholten AWJ, van Leuteren RW, de Waal CG, de Jongh FH, van Kaam AH, Hutten GJ.

Objective: Monitoring heart rate (HR) and respiratory rate (RR) is essential in preterm infants and is currently measured with ECG and chest impedance (CI), respectively. However, in current clinical practice these techniques use wired adhesive electrodes which can cause skin damage and hinder parent-infant interaction. Moreover, CI is not always reliable. We assessed the feasibility of a wireless dry electrode belt to measure HR and RR via transcutaneous diaphragmatic electromyography (dEMG).
Approach: In this prospective, observational study, infants were monitored up to 72 h with the belt and standard CI. Feasibility of the belt was expressed by its ability to retrieve a respiratory waveform from dEMG, determining the percentage of time with stable respiration data without signal errors ('lead-off' and Bluetooth Loss Error, 'BLE'), skin-friendliness of the belt (skin score) and by exploring the ability to monitor trends in HR and RR with the belt.
Main results: In all 19 included infants (median gestational age 27.3 weeks) a respiratory waveform could be obtained. The amount of signal errors was low (lead-off 0.5% (IQR 0.1-1.6) and BLE 0.3% (IQR 0.1-0.9)) and 76.5% (IQR 69.3-80.0) of the respiration measurement was stable. No adverse skin effects were observed (median skin score of 3(3-4)). A similar HR and RR trend between the belt and CI was observed.
Significance: Dry electrodes incorporated in a non-adhesive belt can measure dEMG in preterm infants. The belt provided a HR and RR trend similar to CI. Future studies are required to investigate the non-inferiority of the belt as a cardiorespiratory monitor compared to CI.

Gepubliceerd: Physiol Meas. 2022;43(5).
Impact factor: 2.688 ; Q3

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18. Multicentre paired non-inferiority study of the cardiorespiratory monitoring performance of the wireless and non-adhesive Bambi® belt measuring diaphragm activity in neonates: study protocol
Scholten AWJ, Zhan Z, Niemarkt HJ, Vervoorn M, van Leuteren RW, de Jongh FH, van Kaam AH, van den Heuvel ER, Hutten GJ.

Introduction: Cardiorespiratory monitoring is used in the neonatal intensive care unit (NICU) to assess the clinical status of newborn infants and detect critical deteriorations in cardiorespiratory function. Currently, heart rate (HR) is monitored by electrocardiography (ECG) and respiration by chest impedance (CI). Disadvantages of current monitoring techniques are usage of wired adhesive

electrodes which may damage the skin and hinder care. The Bambi® belt is a wireless and non-adhesive alternative that enables cardiorespiratory monitoring by measuring electrical activity of the diaphragm via transcutaneous electromyography. A previous study showed feasibility of the Bambi® belt and this study compares the belt performance to ECG and CI.
Methods and Analysis: This multicentre non-inferiority paired study will be performed in the NICU of the Máxima Medical Center (MMC) in Veldhoven and the Emma Children's Hospital, Amsterdam University Medical Centre (AmsterdamUMC) in Amsterdam, The Netherlands. 39 infants in different postmenstrual age groups (minimally 10 infants<30 weeks, between 30-32 weeks and >32 weeks) will be recruited. These infants will be monitored with the Bambi® belt in addition to standard ECG and CI for 24 hours. The primary outcome is the HR, studied with three criteria: (1) the limits of agreement of the HR measurements in terms of the second-to-second difference in the HR between the belt and standard ECG, (2) the detection of cardiac events consisting of bradycardia and tachycardia and (3) the quality of HR-monitoring. The secondary outcome is the respiratory rate (RR), studied with the criteria (1) agreement in RR-trend monitoring, (2) apnoea and tachypnoea detection and (3) reliable registrations.
Ethics and Dissemination: This protocol was approved by the Medical Ethical Committee of the MMC and the Central Committee for Human Research. The MMC started patient recruitment in July and the AmsterdamUMC in August 2021. The results will be presented at conferences and published in peer-reviewed journals.
Trial registration number: NL9480.

Gepubliceerd: BMJ Paediatr Open. 2022;6(1).
Impact factor: 2.922; Q2

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19. Self-management interventions for people with chronic obstructive pulmonary disease
Schrijver J, Lenferink A, Brusse-Keizer M, Zwerink M, van der Valk PD, van der Palen J, Effing TW.

Background: Self-management interventions help people with chronic obstructive pulmonary disease (COPD) to acquire and practise the skills they need to carry out disease-specific medical regimens, guide changes in health behaviour and provide emotional support to enable them to control their disease. Since the 2014 update of this review, several studies have been published.
Objectives: Primary objectives To evaluate the effectiveness of COPD self-management interventions compared to usual care in terms of health-related quality of life (HRQoL) and respiratory-related hospital admissions. To evaluate the safety of COPD self-management interventions compared to usual care in terms of respiratory-related mortality and all-cause mortality. Secondary objectives To evaluate the effectiveness of COPD self-management interventions compared to usual care in terms of other health outcomes and healthcare utilisation. To evaluate effective characteristics of COPD self-management interventions.
Search methods: We searched the Cochrane Airways Trials Register, CENTRAL, MEDLINE, EMBASE, trials registries and the reference lists of included studies up until January 2020.
Selection criteria: Randomised controlled trials (RCTs) and cluster-randomised trials (CRTs) published since 1995. To be eligible for inclusion, self-management interventions had to include at least two intervention components and include an iterative process between participant and healthcare provider(s) in which goals were formulated and feedback was given on self-management actions by the participant.
Data collection and analysis: Two review authors independently selected studies for inclusion, assessed trial quality and extracted data. We resolved disagreements by reaching consensus or by involving a third review author. We contacted study authors to obtain additional information and missing outcome data where possible. Primary outcomes were health-related quality of life (HRQoL), number of respiratory-related hospital admissions, respiratory-related mortality, and all-cause

mortality. When appropriate, we pooled study results using random-effects modelling meta-analyses. MAIN RESULTS: We included 27 studies involving 6008 participants with COPD. The follow-up time ranged from two-and-a-half to 24 months and the content of the interventions was diverse. Participants' mean age ranged from 57 to 74 years, and the proportion of male participants ranged from 33% to 98%. The post-bronchodilator forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio of participants ranged from 33.6% to 57.0%. The FEV1/FVC ratio is a measure used to diagnose COPD and to determine the severity of the disease. Studies were conducted on four different continents (Europe (n = 15), North America (n = 8), Asia (n = 1), and Oceania (n = 4); with one study conducted in both Europe and Oceania). Self-management interventions likely improve HRQoL, as measured by the St. George's Respiratory Questionnaire (SGRQ) total score (lower score represents better HRQoL) with a mean difference (MD) from usual care of -2.86 points (95% confidence interval (CI) -4.87 to -0.85; 14 studies, 2778 participants; low-quality evidence). The pooled MD of -2.86 did not reach the SGRQ minimal clinically important difference (MCID) of four points. Self-management intervention participants were also at a slightly lower risk for at least one respiratory-related hospital admission (odds ratio (OR) 0.75, 95% CI 0.57 to 0.98; 15 studies, 3263 participants; very low-quality evidence). The number needed to treat to prevent one respiratory-related hospital admission over a mean of 9.75 months' follow-up was 15 (95% CI 8 to 399) for participants with high baseline risk and 26 (95% CI 15 to 677) for participants with low baseline risk. No differences were observed in respiratory-related mortality (risk difference (RD) 0.01, 95% CI -0.02 to 0.04; 8 studies, 1572 participants ; low-quality evidence) and all-cause mortality (RD -0.01, 95% CI -0.03 to 0.01; 24 studies, 5719 participants; low-quality evidence). We graded the evidence to be of 'moderate' to 'very low' quality according to GRADE. All studies had a substantial risk of bias, because of lack of blinding of participants and personnel to the interventions, which is inherently impossible in a self-management intervention. In addition, risk of bias was noticeably increased because of insufficient information regarding a) non-protocol interventions, and b) analyses to estimate the effect of adhering to interventions. Consequently, the highest GRADE evidence score that could be obtained by studies was 'moderate'.
Conclusions: Self-management interventions for people with COPD are associated with improvements in HRQoL, as measured with the SGRQ, and a lower probability of respiratory-related hospital admissions. No excess respiratory-related and all-cause mortality risks were observed, which strengthens the view that COPD self-management interventions are unlikely to cause harm. By using stricter inclusion criteria, we decreased heterogeneity in studies, but also reduced the number of included studies and therefore our capacity to conduct subgroup analyses. Data were therefore still insufficient to reach clear conclusions about effective (intervention) characteristics of COPD self-management interventions. As tailoring of COPD self-management interventions to individuals is desirable, heterogeneity is and will likely remain present in self-management interventions. For future studies, we would urge using only COPD self-management interventions that include iterative interactions between participants and healthcare professionals who are competent using behavioural change techniques (BCTs) to elicit participants' motivation, confidence and competence to positively adapt their health behaviour(s) and develop skills to better manage their disease. In addition, to inform further subgroup and meta-regression analyses and to provide stronger conclusions regarding effective COPD self-management interventions, there is a need for more homogeneity in outcome measures. More attention should be paid to behavioural outcome measures and to providing more detailed, uniform and transparently reported data on self-management intervention components and BCTs. Assessment of outcomes over the long term is also recommended to capture changes in people's behaviour. Finally, information regarding non-protocol interventions as well as analyses to estimate the effect of adhering to interventions should be included to increase the quality of evidence.

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Impact factor: 11.874; Q1

20. Paediatric COVID-19 mortality: a database analysis of the impact of health resource disparity
Marwali EM, Kekalih A, Yuliarto S, Wati DK, Rayhan M, Valerie IC, Cho HJ, Jassat W, Blumberg L, Masha M, Semple C, Swann OV, Kohns Vasconcelos M, Popielska J, Murthy S, Fowler RA, Guerguerian AM, Streinu-Cercel A, Pathmanathan MD, Rojek A, Kartsonaki C, Goncalves BP, Citarella BW, Merson L, Olliaro PL, Dalton HJ, International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Clinical Characterization Group Investigators; Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, van Veen H, Vonkeman H

Background: The impact of the COVID-19 pandemic on paediatric populations varied between high-income countries (HICs) versus low-income to middle-income countries (LMICs). We sought to investigate differences in paediatric clinical outcomes and identify factors contributing to disparity between countries.
Methods: The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) COVID-19 database was queried to include children under 19 years of age admitted to hospital from January 2020 to April 2021 with suspected or confirmed COVID-19 diagnosis. Univariate and multivariable analysis of contributing factors for mortality were assessed by country group (HICs vs LMICs) as defined by the World Bank criteria.
Results: A total of 12 860 children (3819 from 21 HICs and 9041 from 15 LMICs) participated in this study. Of these, 8961 were laboratory-confirmed and 3899 suspected COVID-19 cases. About 52% of LMICs children were black, and more than 40% were infants and adolescent. Overall in-hospital mortality rate (95% CI) was 3.3% [=(3.0% to 3.6%), higher in LMICs than HICs (4.0% (3.6% to 4.4%) and 1.7% (1.3% to 2.1%), respectively). There were significant differences between country income groups in intervention profile, with higher use of antibiotics, antivirals, corticosteroids, prone positioning, high flow nasal cannula, non-invasive and invasive mechanical ventilation in HICs. Out of the 439 mechanically ventilated children, mortality occurred in 106 (24.1%) subjects, which was higher in LMICs than HICs (89 (43.6%) vs 17 (7.2%) respectively). Pre-existing infectious comorbidities (tuberculosis and HIV) and some complications (bacterial pneumonia, acute respiratory distress syndrome and myocarditis) were significantly higher in LMICs compared with HICs. On multivariable analysis, LMIC as country income group was associated with increased risk of mortality (adjusted HR 4.73 (3.16 to 7.10)).
Conclusion: Mortality and morbidities were higher in LMICs than HICs, and it may be attributable to differences in patient demographics, complications and access to supportive and treatment modalities.

Gepubliceerd: BMJ Paediatr Open. 2022;6(1).
Impact factor: 2.922; Q2

Totale impact factor: 202.870
Gemiddelde impact factor: 10.143

Aantal artikelen 1e, 2e of laatste auteur: 6
Totale impact factor: 35.509
Gemiddelde impact factor: 5.918

MDL

1. Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With High Risk for Postoperative Complications: Results of a Randomized Clinical Trial
Berkel AEM, Bongers BC, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, Wymenga M, Bigirwamungu-Bargeman M, van der Palen J, van Det MJ, van Meeteren NLU, Klaase JM.

Objective: To assess the effects of a 3-week community-based exercise program on 30-day postoperative complications in high-risk patients scheduled for elective colorectal resection for (pre)malignancy.
Background data: Patients with a low preoperative aerobic fitness undergoing colorectal surgery have an increased risk of postoperative complications. It remains, however, to be demonstrated whether prehabilitation in these patients reduces postoperative complications**.**
Methods: This 2-center, prospective, single-blinded randomized clinical trial was carried out in 2 large teaching hospitals in the Netherlands. Patients (≥60 years) with colorectal (pre)malignancy scheduled for elective colorectal resection and with a score ≤7 metabolic equivalents on the veterans-specific activity questionnaire were randomly assigned to the prehabilitation group or the usual care group by using block-stratified randomization. An oxygen uptake at the ventilatory anaerobic threshold <11 mL/kg/min at the baseline cardiopulmonary exercise test was the final inclusion criterion. Inclusion was based on a power analysis. Patients in the prehabilitation group participated in a personalized 3-week (3 sessions per week, nine sessions in total) supervised exercise program given in community physical therapy practices before colorectal resection. Patients in the reference group received usual care. The primary outcome was the number of patients with one or more complications within 30 days of surgery, graded according to the Clavien-Dindo classification. Data were analyzed on an intention-to-treat basis**.**
Results: Between February 2014 and December 2018, 57 patients [30 males and 27 females; mean age 73.6 years (standard deviation 6.1), range 61-88 years] were randomized to either prehabilitation (n = 28) or usual care (n = 29). The rate of postoperative complications was lower in the prehabilitation group (n = 12, 42.9%) than in the usual care group (n = 21, 72.4%, relative risk 0.59, 95% confidence interval 0.37-0.96, P = 0.024).
Conclusions: Exercise prehabilitation reduced postoperative complications in high-risk patients scheduled to undergo elective colon resection for (pre)malignancy. Prehabilitation should be considered as usual care in high-risk patients scheduled for elective colon, and probably also rectal, surgery.

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Impact factor: 13.787 ; Q1

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2. Factors influencing endoscopic estimation of colon polyp size in a colon model
Beukema KR, Simmering JA, Brusse-Keizer M, John S, Quispel R, Mensink PB.

Background/Aims: Colorectal polyps are removed to prevent progression to colorectal cancer. Polyp size is an important factor for risk stratification of malignant transformation. Endoscopic size estimation correlates poorly with pathological reports and several factors have been suggested to influence size estimation. We aimed to gain insight into the factors influencing endoscopic polyp size estimation**.**
Methods: Images of polyps in an artificial model were obtained at 1, 3, and 5 cm from the colonoscope's tip. Participants were asked to estimate the diameter and volume of each polyp**.**
Results: Fifteen endoscopists from three large-volume centers participated in this study. With an intraclass correlation coefficient of 0.66 (95% confidence interval [CI], 0.62-0.71) for diameter and

0.56 (95% CI, 0.50-0.62) for volume. Polyp size estimated at 3 cm from the colonoscope's tip yielded the best results. A lower distance between the tip and the polyp was associated with a larger estimated polyp size**.**
Conclusion: Correct endoscopic estimation of polyp size remains challenging. This finding can affect size estimation skills and future training programs for endoscopists.

Gepubliceerd: Clin Endosc. 2022;55(4):540-8.
Impact factor: 0 ; Q NVT

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3. Aminotransferases During Treatment Predict Long-Term Survival in Patients With Autoimmune Hepatitis Type 1: A Landmark Analysis
Biewenga M, Verhelst X, Baven-Pronk M, Putter H, van den Berg A, Colle I, Schouten J, Sermon F, Van Steenkiste C, van Vlierberghe H, van der Meer A, van Hoek B, Dutch Autoimmune Hepatitis Study Group; Guichelaar MMJ.

Background & Aims: Biochemical remission, important treatment goal in autoimmune hepatitis (AIH), has been associated with better long-term survival. The aim of this study was to determine the independent prognostic value of aminotransferases and immunoglobulin G (IgG) during treatment on long-term transplant-free survival in AIH**.**
Methods: In a multicenter cohort alanine aminotransferase, aspartate aminotransferase (AST), and IgG were collected at diagnosis and 6, 12, 24, and 36 months after start of therapy and related to long-term outcome using Kaplan-Meier survival and Cox regression analysis with landmark analysis at these time points, excluding patients with follow-up ending before each landmark**.**
Results: A total of 301 AIH patients with a median follow-up of 99 (range, 7-438) months were included. During follow-up, 15 patients required liver transplantation and 33 patients died. Higher AST at 12 months was associated with worse survival (hazard ratio [HR], 1.86; P < .001), while IgG was not associated with survival (HR, 1.30; P = .53). In multivariate analysis AST at 12 months (HR, 2.13; P < .001) was predictive for survival independent of age, AST at diagnosis and cirrhosis. Multivariate analysis for AST yielded similar results at 6 months (HR, 2.61; P = .001), 24 months (HR, 2.93; P = .003), and 36 months (HR, 3.03; P = .010). There was a trend toward a worse survival in patients with mildly elevated aminotransferases (1-1.5× upper limit of normal) compared with patients with normal aminotransferases (P = .097).
Conclusions: Low aminotransferases during treatment are associated with a better long-term survival in autoimmune hepatitis. IgG was not associated with survival in first 12 months of treatment. Normalization of aminotransferases should be the treatment goal for autoimmune hepatitis to improve long-term survival.

Gepubliceerd: Clin Gastroenterol Hepatol. 2022;20(8):1776-83.e4.
Impact factor: 13.576; Q1

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4. The Effect of Phenotype and Genotype on the Plasma Proteome in Patients with Inflammatory Bowel Disease
Bourgonje AR, Hu S, Spekhorst LM, Zhernakova DV, Vich Vila A, Li Y, Voskuil MD, van Berkel LA, Bley Folly B, Charrout M, Mahfouz A, Reinders MJT, van Heck JIP, Joosten LAB, Visschedijk MC, van Dullemen HM, Faber KN, Samsom JN, Festen EAM, Dijkstra G, Weersma RK.

Background and Aims: Protein profiling in patients with inflammatory bowel diseases [IBD] for diagnostic and therapeutic purposes is underexplored. This study analysed the association between phenotype, genotype, and the plasma proteome in IBD**.**

Methods: A total of 92 inflammation-related proteins were quantified in plasma of 1028 patients with IBD (567 Crohn's disease [CD]; 461 ulcerative colitis [UC]) and 148 healthy individuals to assess protein-phenotype associations. Corresponding whole-exome sequencing and global screening array data of 919 patients with IBD were included to analyse the effect of genetics on protein levels (protein quantitative trait loci [pQTL] analysis). Intestinal mucosal RNA sequencing and faecal metagenomic data were used for complementary analyses**.**
Results: Thirty-two proteins were differentially abundant between IBD and healthy individuals, of which 22 proteins were independent of active inflammation; 69 proteins were associated with 15 demographic and clinical factors. Fibroblast growth factor-19 levels were decreased in CD patients with ileal disease or a history of ileocecal resection. Thirteen novel cis-pQTLs were identified and 10 replicated from previous studies. One trans-pQTL of the fucosyltransferase 2 [FUT2] gene [rs602662] and two independent cis-pQTLs of C-C motif chemokine 25 [CCL25] affected plasma CCL25 levels. Intestinal gene expression data revealed an overlapping cis-expression [e]QTL-variant [rs3745387] of the CCL25 gene. The FUT2 rs602662 trans-pQTL was associated with reduced abundances of faecal butyrate-producing bacteria.
Conclusions: This study shows that genotype and multiple disease phenotypes strongly associate with the plasma inflammatory proteome in IBD, and identifies disease-associated pathways that may help to improve disease management in the future.

Gepubliceerd: J Crohns Colitis. 2022;16(3):414-29.
Impact factor: 10.020 ; Q1

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5. Proteomic analyses do not reveal subclinical inflammation in fatigued patients with clinically quiescent inflammatory bowel disease
Bourgonje AR, Wichers SJ, Hu S, van Dullemen HM, Visschedijk MC, Faber KN, Festen EAM, Dijkstra G, Samsom JN, Weersma RK, Spekhorst LM.

Fatigue is a common and clinically challenging symptom in patients with inflammatory bowel diseases (IBD), occurring in ~ 50% of patients with quiescent disease. In this study, we aimed to investigate whether fatigue in patients with clinically quiescent IBD is reflected by circulating inflammatory proteins, which might reflect ongoing subclinical inflammation. Ninety-two (92) different inflammation-related proteins were measured in plasma of 350 patients with clinically quiescent IBD. Quiescent IBD was defined as clinical (Harvey-Bradshaw Index < 5 or Simple Clinical Colitis Activity Index < 2.5) and biochemical remission (C-reactive protein < 5 mg/L and absence of anemia) at time of fatigue assessment. Leukemia inhibitory factor receptor (LIF-R) concentrations were inversely associated with severe fatigue, also after adjustment for confounding factors (nominal $P < 0.05$). Although solely LIF-R showed weak ability to discriminate between mild and severe fatigue (area under the curve [AUC] = 0.61, 95%CI: 0.53-0.69, $P < 0.05$), a combined set of the top seven (7) fatigue-associated proteins (all $P < 0.10$) was observed to have reasonable discriminative performance (AUC = 0.82 [95%CI: 0.74-0.91], $P < 0.01$). Fatigue in patients with IBD is not clearly reflected by distinct protein signatures, suggesting there is no subclinical inflammation defined by the studied inflammatory proteins. Future studies are warranted to investigate other proteomic markers that may reflect fatigue in clinically quiescent IBD.

Gepubliceerd: Sci Rep. 2022;12(1):14581.
Impact factor: 4.997 ; Q2

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6. Jaundice due to a rare cause: detection through systematic analysis
Doornebosch VLE, van Baarlen J, Venneman NG.

Background: Jaundice is a clinical symptom as a result of cholestasis. It can be caused by a wide variety of disorders. Its differential diagnosis is broad. Therefore, it is important to determine whether the cause of the cholestasis is intrahepatic, hepatic or extrahepatic.
Case description: This article describes a 61-year-old male who was referred to our Gastroenterology Department. Transabdominal ultrasound showed dilatation of intrahepatic bile ducts and the common bile duct, probably caused by a sludge ball. He underwent an ERCP during which a mass instead of a gallstone was extracted. Histological examination showed (a metastasis of) a melanoma. The patient was referred to the dermatologist who found a melanoma on the chest. The final diagnosis was metastasis of melanoma to the common bile duct**.**
Conclusion: Jaundice can be caused by a variety of disorders. A systematic approach based on signs and symptoms is essential to recognize uncommon diagnoses without unnecessary delay.

Gepubliceerd: Ned Tijdschr Geneeskd. 2022;166.
Impact factor: 0 ; Q NVT

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7. Recurrent Cholecystitis Due to Gallstone Obstruction of a Lumen-Apposing Metal Stent
Geertsema S, Meinds RJ, Venneman NG.

Gepubliceerd: Clin Gastroenterol Hepatol. 2022;20(10):A28.
Impact factor: 13.576; Q1

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8. Hepatitis C Elimination in the Netherlands (CELINE): How nationwide retrieval of lost to follow-up hepatitis C patients contributes to micro-elimination
Isfordink CJ, van Dijk M, Brakenhoff SM, Kracht PAM, Arends JE, de Knegt RJ, van der Valk M, Drenth JPH, CELINE Study Group; Venneman N.G, Bosma F.

Background & Aims: The number of chronic hepatitis C virus (HCV)-infected patients who have been lost to follow-up (LTFU) is high and threatens HCV elimination. Micro-elimination focusing on the LTFU population is a promising strategy for low-endemic countries like the Netherlands (HCV prevalence 0.16%). We therefore initiated a nationwide retrieval project in the Netherlands targeting LTFU HCV patients**.**
Methods: LTFU HCV-infected patients were identified using laboratory and patient records. Subsequently, the Municipal Personal Records database was queried to identify individuals eligible for retrieval, defined as being alive and with a known address in the Netherlands. These individuals were invited for re-evaluation. The primary endpoint was the number of patients successfully re-linked to care**.**
Results: Retrieval was implemented in 45 sites in the Netherlands. Of 20,183 ever-diagnosed patients, 13,198 (65%) were known to be cured or still in care and 1,537 (8%) were LTFU and eligible for retrieval. Contact was established with 888/1,537 (58%) invited individuals; 369 (24%) had received prior successful treatment elsewhere, 131 (9%) refused re-evaluation and 251 (16%) were referred for re-evaluation. Finally, 219 (14%) were re-evaluated, of whom 172 (79%) approved additional data collection. HCV-RNA was positive in 143/172 (83%), of whom 38/143 (27%) had advanced fibrosis or cirrhosis and 123/143 (86%) commenced antiviral treatment**.**
Conclusion: Our nationwide micro-elimination strategy accurately mapped the ever-diagnosed HCV population in the Netherlands and indicates that 27% of LTFU HCV-infected patients re-linked to care have advanced fibrosis or cirrhosis. This emphasizes the potential value of systematic retrieval for HCV elimination.

Gepubliceerd: Eur J Intern Med. 2022;101:93-7.
Impact factor: 7.749 ; Q1

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9. Systematic Review of the Efficacy of Treatment for Median Arcuate Ligament Syndrome
Metz FM, Blauw JTM, Brusse-Keizer M, Kolkman JJ, Bruno MJ, Geelkerken RH.

Objective: Since the first description of the median arcuate ligament syndrome (MALS), the existence for the syndrome and the efficacy of treatment for it have been questioned**.**
Methods: A systematic review conforming to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement was conducted, with a broader view on treatment for MALS including any kind of coeliac artery release, coeliac plexus resection, and coeliac plexus blockage, irrespective of age. Online databases were used to identify papers published between 1963 and July 2021. The inclusion criteria were abdominal symptoms, proof of MALS on imaging, and articles reporting at least three patients. Primary outcomes were symptom relief and quality of life (QoL)**.**
Results: Thirty-eight studies describing 880 adult patients and six studies describing 195 paediatric patients were included. The majority of the adult studies reported symptom relief of more than 70% from three to 228 months after treatment. Two adult studies showed an improved QoL after treatment. Half of the paediatric studies reported symptom relief of more than 70% from six to 62 months after laparoscopic coeliac artery release, and four studies reported an improved QoL. Thirty-five (92%) adult studies and five (83%) paediatric studies scored a high or unclear risk of bias for the majority of the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) items. The meaning of coeliac plexus resection or blockage could not be substantiated**.**
Conclusion: This systematic review suggests a sustainable symptom relief of more than 70% after treatment for MALS in the majority of adult and paediatric studies; however, owing to the heterogeneity of the inclusion criteria and outcome parameters, the risk of bias was high and a formal meta-analysis could not be performed. To improve care for patients with MALS the next steps would be to deal with reporting standards, outcome definitions, and consensus descriptions of the intervention(s), after which an appropriate randomised controlled trial should be performed.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2022;64(6):720-32.
Impact factor: 6.427 ; Q1

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10. Endoscopic Versus Surgical Step-Up Approach for Infected Necrotizing Pancreatitis (ExTENSION): Long-term Follow-up of a Randomized Trial
Onnekink AM, Boxhoorn L, Timmerhuis HC, Bac ST, Besselink MG, Boermeester MA, Bollen TL, Bosscha K, Bouwense SAW, Bruno MJ, van Brunschot S, Cappendijk VC, Consten ECJ, Dejong CH, Dijkgraaf MGW, van Eijck CHJ, Erkelens WG, van Goor H, van Grinsven J, Haveman JW, van Hooft JE, Jansen JM, van Lienden KP, Meijssen MAC, Nieuwenhuijs VB, Poley JW, Quispel R, de Ridder RJ, Römkens TEH, van Santvoort HC, Scheepers JJ, Schwartz MP, Seerden T, Spanier MBW, Straathof JWA, Timmer R, Venneman NG, Verdonk RC, Vleggaar FP, van Wanrooij RL, Witteman BJM, Fockens P, Voermans RP.

Background & Aims: Previous randomized trials, including the Transluminal Endoscopic Step-Up Approach Versus Minimally Invasive Surgical Step-Up Approach in Patients With Infected Pancreatic Necrosis (TENSION) trial, demonstrated that the endoscopic step-up approach might be preferred over the surgical step-up approach in patients with infected necrotizing pancreatitis based on favorable short-term outcomes. We compared long-term clinical outcomes of both step-up approaches after a period of at least 5 years**.**

Methods: In this long-term follow-up study, we reevaluated all clinical data on 83 patients (of the originally 98 included patients) from the TENSION trial who were still alive after the initial 6-month follow-up. The primary end point, similar to the TENSION trial, was a composite of death and major complications. Secondary end points included individual major complications, pancreaticocutaneous fistula, reinterventions, pancreatic insufficiency, and quality of life**.**
Results: After a mean follow-up period of 7 years, the primary end point occurred in 27 patients (53%) in the endoscopy group and in 27 patients (57%) in the surgery group (risk ratio [RR], 0.93; 95% confidence interval [CI], 0.65-1.32; P = .688). Fewer pancreaticocutaneous fistulas were identified in the endoscopy group (8% vs 34%; RR, 0.23; 95% CI, 0.08-0.83). After the initial 6-month follow-up, the endoscopy group needed fewer reinterventions than the surgery group (7% vs 24%; RR, 0.29; 95% CI, 0.09-0.99). Pancreatic insufficiency and quality of life did not differ between groups.
Conclusions: At long-term follow-up, the endoscopic step-up approach was not superior to the surgical step-up approach in reducing death or major complications in patients with infected necrotizing pancreatitis. However, patients assigned to the endoscopic approach developed overall fewer pancreaticocutaneous fistulas and needed fewer reinterventions after the initial 6-month follow-up. Netherlands Trial Register no: NL8571.

Gepubliceerd: Gastroenterology. 2022;163(3):712-22.e14.
Impact factor: 33.883 ; Q1

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11. Favourable Tolerability and Drug Survival of Tioguanine Versus Methotrexate After Failure of Conventional Thiopurines in Crohn's Disease
Savelkoul EHJ, Maas MHJ, Bourgonje AR, Crouwel F, Biemans VBC, den Broeder N, Russel M, Römkens TEH, de Boer NK, Dijkstra G, Hoentjen F.

Background and Aims: Both methotrexate and tioguanine can be considered as treatment options in patients with Crohn's disease after failure of conventional thiopurines. This study aimed to compare tolerability and drug survival of methotrexate and tioguanine therapy after failure of conventional thiopurines in patients with Crohn's disease**.**
Methods: We conducted a retrospective, multicentre study, including patients with Crohn's disease initiating monotherapy methotrexate or tioguanine after failure [all causes] of conventional thiopurines. Follow-up duration was 104 weeks or until treatment discontinuation. The primary outcome was cumulative therapy discontinuation incidence due to adverse events. Secondary outcomes included total number of [serious] adverse events, and ongoing monotherapy**.**
Results: In total, 219 patients starting either methotrexate [n = 105] or tioguanine [n = 114] were included. In all 65 [29.7%] patients (methotrexate 43.8% [46/105 people], tioguanine 16.7% [19/114 people], p <0.001) discontinued their treatment due to adverse events during follow-up. Median time until discontinuation due to adverse events was 16 weeks (interquartile range [IQR] 7-38, p = 0.812). Serious adverse events were not significantly different. Patients treated with methotrexate experienced adverse events more often [methotrexate 83%, tioguanine 46%, p <0.001]. Total monotherapy drug survival after 104 weeks was 22% for methotrexate and 46% for tioguanine [p <0.001].
Conclusions: We observed a higher cumulative discontinuation incidence due to adverse events for methotrexate [44%] compared with tioguanine [17%] in Crohn's disease patients after failure of conventional thiopurines. The total adverse events incidence during methotrexate use was higher, whereas serious adverse events incidence was similar. These favourable results for tioguanine treatment may guide the selection of immunosuppressive therapy after failure of conventional thiopurines.

Gepubliceerd: J Crohns Colitis. 2022;16(9):1372-9.

Impact factor: 10.020 ; Q1

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12. Assessing the efficacy and safety of mycophenolate mofetil versus azathioprine in patients with autoimmune hepatitis (CAMARO trial): study protocol for a randomised controlled trial
Snijders R, Stoelinga AEC, Gevers TJG, Pape S, Biewenga M, Verdonk RC, de Jonge HJM, Vrolijk JM, Bakker SF, Vanwolleghem T, de Boer YS, Pronk M, Beuers UHW, van der Meer AJ, van Gerven NMF, Sijtsma MGM, Verwer BJ, Gisbertz IAM, Bartelink M, van den Brand FF, Sebib Korkmaz K, van den Berg AP, Guichelaar MMJ, Soufidi K, Levens AD, van Hoek B, Drenth JPH.

Background: Currently, the standard therapy for autoimmune hepatitis (AIH) consists of a combination of prednisolone and azathioprine. However, 15% of patients are intolerant to azathioprine which necessitates cessation of azathioprine or changes in therapy. In addition, not all patients achieve complete biochemical response (CR). Uncontrolled data indicate that mycophenolate mofetil (MMF) can induce CR in a majority of patients. Better understanding of first-line treatment and robust evidence from randomised clinical trials are needed. The aim of this study was to explore the potential benefits of MMF as compared to azathioprine, both combined with prednisolone, as induction therapy in a randomised controlled trial in patients with treatment-naive AIH**.**
Methods: CAMARO is a randomised (1:1), open-label, parallel-group, multicentre superiority trial. All patients with AIH are screened for eligibility. Seventy adult patients with AIH from fourteen centres in the Netherlands and Belgium will be randomised to receive MMF or azathioprine. Both treatment arms will start with prednisolone as induction therapy. The primary outcome is biochemical remission, defined as serum levels of alanine aminotransferase and immunoglobulin G below the upper limit of normal. Secondary outcomes include safety and tolerability of MMF and azathioprine, time to remission, changes in Model For End-Stage Liver Disease (MELD)-score, adverse events, and aspects of quality of life. The study period will last for 24 weeks.
Discussion: The CAMARO trial investigates whether treatment with MMF and prednisolone increases the proportion of patients in remission compared with azathioprine and prednisolone as the current standard treatment strategy. In addition, we reflect on the challenges of conducting a randomized trial in rare diseases.
Trial registration: EudraCT 2016-001038-91 . Prospectively registered on 18 April 2016.

Gepubliceerd: Trials. 2022;23(1):1012.
Impact factor: 2.728 ; Q4

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13. Performance of diagnostic tools for acute cholangitis in patients with suspected biliary obstruction
Sperna Weiland CJ, Busch CBE, Bhalla A, Bruno MJ, Fockens P, van Hooft JE, Poen AC, Timmerhuis HC, Umans DS, Venneman NG, Verdonk RC, Drenth JPH, de Wijkerslooth TR, van Geenen EJM.

Background: Acute cholangitis is an infection requiring endoscopic retrograde cholangiopancreatography (ERCP) and antibiotics. Several diagnostic tools help to diagnose cholangitis. Because diagnostic performance of these tools has not been studied and might therefore impose unnecessary ERCPs, we aimed to evaluate this**.**
Methods: We established a nationwide prospective cohort of patients with suspected biliary obstruction who underwent an ERCP. We assessed the diagnostic performance of Tokyo Guidelines (TG18), Dutch Pancreatitis Study Group (DPSG) criteria, and Charcot triad relative to real-world cholangitis as the reference standard**.**

Results: 127 (16%) of 794 patients were diagnosed with real-world cholangitis. Using the TG18, DPSG, and Charcot triad, 345 (44%), 55 (7%), and 66 (8%) patients were defined as having cholangitis, respectively. Sensitivity for TG18 was 82% (95% CI 74-88) and specificity 60% (95% CI 56-63). The sensitivity for DPSG and Charcot was 42% (95% CI 33-51) and 46% (95% CI 38-56), specificity was 99.7% (95% CI 99-100) and 99% (95% CI 98-100), respectively.
Conclusions: TG18 criteria incorrectly diagnoses four out of ten patients with real-world cholangitis, while DPSG and Charcot criteria failed to diagnose more than half of patients. As the cholangitis diagnosis has many consequences for treatment, there is a need for more accurate diagnostic tools or work-up towards ERCP.

Gepubliceerd: J Hepatobiliary Pancreat Sci. 2022;29(4):479-86.
Impact factor: 3.149 ; Q2

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14. Optimal timing of rectal diclofenac in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis
Sperna Weiland CJ, Smeets X, Verdonk RC, Poen AC, Bhalla A, Venneman NG, Kievit W, Timmerhuis HC, Umans DS, van Hooft JE, Besselink MG, van Santvoort HC, Fockens P, Bruno MJ, Drenth JPH, van Geenen EJM.

Background and study aims: Rectal nonsteroidal anti-inflammatory drug (NSAID) prophylaxis reduces incidence of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Direct comparisons to the optimal timing of administration, before or after ERCP, are lacking. Therefore, we aimed to assess whether timing of rectal NSAID prophylaxis affects the incidence of post-ERCP pancreatitis.
Patients and methods: We conducted an analysis of prospectively collected data from a randomized clinical trial. We included patients with a moderate to high risk of developing post-ERCP pancreatitis, all of whom received rectal diclofenac monotherapy 100-mg prophylaxis. Administration was within 30 minutes before or after the ERCP at the discretion of the endoscopist. The primary endpoint was post-ERCP pancreatitis. Secondary endpoints included severity of pancreatitis, length of hospitalization, and Intensive Care Unit (ICU) admittance.
Results: We included 346 patients who received the rectal NSAID before ERCP and 63 patients who received it after ERCP. No differences in baseline characteristics were observed. Post-ERCP pancreatitis incidence was lower in the group that received pre-procedure rectal NSAIDs (8 %), compared to post-procedure (18 %) (relative risk: 2.32; 95% confidence interval: 1.21 to 4.46, P = 0.02). Hospital stays were significantly longer with post-procedure prophylaxis (1 day; interquartile range [IQR] 1-2 days vs. 1 day; IQR 1-4 days; P = 0.02). Patients from the post-procedure group were more likely to be admitted to the ICU (1 patient [0.3 %] vs. 4 patients [6 %]; P = 0.002).
Conclusions: Pre-procedure administration of rectal diclofenac is associated with a significant reduction in post-ERCP pancreatitis incidence compared to post-procedure use.

Gepubliceerd: Endosc Int Open. 2022;10(3):E246-e53.
Impact factor: 0 ; Q NVT

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15. Commentary: Intermittent Fasting and Akkermansia Muciniphila Potentiate the Antitumor Efficacy of FOLFOX in Colon Cancer
Su J, Braat H, Verhaar A, Peppelenbosch M.

Gepubliceerd: Front Pharmacol. 2022;13:843133.
Impact factor: 5.988 ; Q1

16. Impact of Biological Therapies and Tofacitinib on Real-world Work Impairment in Inflammatory Bowel Disease Patients: A Prospective Study
Thomas PWA, den Broeder N, Derikx M, Kievit W, West RL, Russel M, Jansen JM, Römkens TEH, Hoentjen F.

Background: There are limited real-world data on the change in total work impairment (TWI) in biological-treated patients with inflammatory bowel disease (IBD). This study aimed to evaluate the real-world effects of initiating biological therapy or tofacitinib on change in TWI in IBD patients**.**
Methods: This multicenter prospective cohort study enrolled IBD patients who started treatment with biological therapy or tofacitinib. Subjects completed the work productivity and activity impairment (WPAI) questionnaire and short inflammatory bowel disease questionnaire at therapy initiation and at week 26. Total work impairment comprises working hours missed due to sick leave and impact of disease during working hours (range 0%-100%). Clinical disease activity was assessed using the Harvey-Bradshaw Index and Simple Clinical Colitis Activity Index (SCCAI)**.**
Results: We included 137 IBD patients for analyses (median age 38 years, 58% Crohn's disease [CD]). The median baseline TWI was 50% and decreased by a median of 10%-points of points after 26 weeks. Patients with continued biological therapy or tofacitinib use, clinical disease activity at baseline, and clinical response or remission at week 26 showed a greater median TWI reduction (22%-points) than the remaining study patients (7%-points; P = .014). Ulcerative colitis (UC) and IBD-unclassified (IBD-U) patients showed a greater median TWI reduction (26%-points) than CD patients (6%-points); P = .041. Correlations were observed between decrease in TWI and decrease in SCCAI, decrease in fatigue and increase in quality of life.
Conclusions: Work impairment in IBD patients decreased following biological therapy or tofacitinib initiation. Patients achieving clinical remission or response showed the greatest improvement, especially UC and IBD-U patients.

Gepubliceerd: Inflamm Bowel Dis. 2022;28(12):1813-20.
Impact factor: 7.290 ; Q1

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17. De-escalation of biological therapy in inflammatory bowel disease patients following prior dose escalation
Thomas PWA, Smits LJT, Te Groen M, West RL, Russel M, Jansen JM, Römkens TEH, Hoentjen F.

Background: Limited data are available on biological therapy de-escalation after prior escalation in inflammatory bowel disease (IBD) patients. This study aimed to assess the frequency and success rate of de-escalation of biological therapy in IBD patients after prior dose escalation and to evaluate which measures are used to guide de-escalation**.**
Methods: This multicentre retrospective cohort study enrolled IBD patients treated with infliximab (IFX), adalimumab (ADA) or vedolizumab (VEDO) in whom therapy was de-escalated after prior biological escalation. De-escalations were considered pharmacokinetic-driven if based on clinical symptoms combined with therapeutic or supratherapeutic trough levels, and disease activity-driven if based on faecal calprotectin less than or equal to 200 µg/g or resolution of perianal fistula drainage or closure or endoscopic remission. Successful de-escalation was defined as remaining on the same or lower biological dose for greater than or equal to 6 months after de-escalation without the need for corticosteroids**.**
Results: In total, 206 IFX users, 85 ADA users and 55 VEDO users underwent therapy escalation. Of these patients, 34 (17%) on IFX, 18 (21%) on ADA and 8 (15%) on VEDO underwent therapy de-escalation. De-escalation was successful in 88% of IFX patients, 89% of ADA and 100% of VEDO. The

probability of remaining on the de-escalated regimen or further de-escalation after 1 year was 85% for IFX, 62% for ADA and 100% for VEDO. Disease activity-driven de-escalations were more often successful (97%) than pharmacokinetic- and no marker-driven de-escalations (76%); P = 0.017**.**
Conclusion: De-escalation after biological dose escalation was successful in the majority of carefully selected IBD patients. Objective assessment of remission increased the likelihood of successful de-escalation.

Gepubliceerd: Eur J Gastroenterol Hepatol. 2022;34(5):488-95.
Impact factor: 2.586 ; Q4

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18. New Therapeutic Approach for Intestinal Fibrosis Through Inhibition of pH-Sensing Receptor GPR4
Weder B, Schefer F, van Haaften WT, Patsenker E, Stickel F, Mueller S, Hutter S, Schuler C, Baebler K, Wang Y, Mamie C, Dijkstra G, de Vallière C, Imenez Silva PH, Wagner CA, Frey-Wagner I, Ruiz PA, Seuwen K, Rogler G, Hausmann M.

Background: Patients suffering from inflammatory bowel diseases (IBDs) express increased mucosal levels of pH-sensing receptors compared with non-IBD controls. Acidification leads to angiogenesis and extracellular matrix remodeling. We aimed to determine the expression of pH-sensing G protein-coupled receptor 4 (GPR4) in fibrotic lesions in Crohn's disease (CD) patients. We further evaluated the effect of deficiency in Gpr4 or its pharmacologic inhibition**.**
Methods: Paired samples from fibrotic and nonfibrotic terminal ileum were obtained from CD patients undergoing ileocaecal resection. The effects of Gpr4 deficiency were assessed in the spontaneous Il-10-/- and the chronic dextran sodium sulfate (DSS) murine colitis model. The effects of Gpr4 deficiency and a GPR4 antagonist (39c) were assessed in the heterotopic intestinal transplantation model**.**
Results: In human terminal ileum, increased expression of fibrosis markers was accompanied by an increase in GPR4 expression. A positive correlation between the expression of procollagens and GPR4 was observed. In murine disease models, Gpr4 deficiency was associated with a decrease in angiogenesis and fibrogenesis evidenced by decreased vessel length and expression of Edn, Vegfα, and procollagens. The heterotopic animal model for intestinal fibrosis, transplanted with terminal ileum from Gpr4-/- mice, revealed a decrease in mRNA expression of fibrosis markers and a decrease in collagen content and layer thickness compared with grafts from wild type mice. The GPR4 antagonist decreased collagen deposition. The GPR4 expression was also observed in human and murine intestinal fibroblasts. The GPR4 inhibition reduced markers of fibroblast activation stimulated by low pH, notably Acta2 and cTgf.
Conclusions: Expression of GPR4 positively correlates with the expression of profibrotic genes and collagen. Deficiency of Gpr4 is associated with a decrease in angiogenesis and fibrogenesis. The GPR4 antagonist decreases collagen deposition. Targeting GPR4 with specific inhibitors may constitute a new treatment option for IBD-associated fibrosis.

Gepubliceerd: Inflamm Bowel Dis. 2022;28(1):109-25.
Impact factor: 7.290 ; Q1

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19. Lower Risk of Recurrence with a Higher Induction Dose of Mesalazine and Longer Duration of Treatment in Ulcerative Colitis: Results from the Dutch, Non-Interventional, IMPACT Study
West R, Russel M, Bodelier A, Kuijvenhoven J, Bruin K, Jansen J, Van der Meulen A, Keulen E, Wolters L, Ouwendijk R, Bezemer G, Koussoulas V, Tang T, Van Dobbenburgh A, Van Nistelrooy M, Minderhoud I, Vandebosch S, Lubbinge H.

Background and Aims: The dose and duration of mesalazine treatment for ulcerative colitis (UC) is a potentially important determinant of effectiveness, with evidence suggesting that continuing the induction dose for 6-12 months may improve outcomes; however, real-world data are lacking. We assessed mesalazine use in Dutch clinical practice, including how differences in dose and duration affected UC outcomes**.**
Methods: Adults with mild-to-moderate UC who received oral prolonged-release mesalazine de novo or had a dose escalation for an active episode were followed for 12 months in this non-interventional study (ClinicalTrials.gov identifier: NCT02261636). The primary endpoint was time from start of treatment to dose reduction (TDR). Secondary endpoints included recurrence rate, adherence, and work productivity**.**
Results: In total, 151 patients were enrolled, of whom 108 (71.5%) were newly diagnosed with UC. The majority (120; 79.5%) received a dose of ≥4 g/day. Nearly one-third (48; 31.8%) underwent dose reduction, with mean TDR being 8.3 months. Disease extent and endoscopic appearance did not influence duration of induction therapy, while TDR increased with higher baseline UCDAI scores. TDR was longer in patients without (mean 8.8 months) than with (4.1 months) recurrence, although not significantly (p=0.09). Patients on ≥4 g/day had a significantly lower chance of recurrence versus those on 2-<4 g/day (26.6% vs 62.5%, respectively; p=0.04). Longer treatment duration was associated with significantly reduced recurrence risk [hazard ratio >6 months vs 3-6 months: 0.19 (95%CI: 0.08-0.46); p<0.05], particularly for those on ≥4 g/day [0.15 (0.06-0.40) vs 0.26 (0.01-11.9) for 2-<4 g/day). Patients reported significantly increased work productivity, which was maintained throughout follow-up.
Conclusions: Mesalazine was effective induction therapy, with treatment duration not meaningfully influenced by disease extent and endoscopic appearance at initiation. A higher induction dose of oral mesalazine (≥4 g/day) and longer duration of treatment (>6 months) was associated with a lower recurrence risk.

Gepubliceerd: J Gastrointestin Liver Dis. 2022;31(1):18-24.
Impact factor: 2.142 ; Q4

Totale impact factor: 145.208
Gemiddelde impact factor: 7.643

Aantal artikelen 1e, 2e of laatste auteur: 6
Totale impact factor: 26.703
Gemiddelde impact factor: 4.451

Medical School Twente

1. Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With High Risk for Postoperative Complications: Results of a Randomized Clinical Trial
Berkel AEM, Bongers BC, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM, Wymenga M, Bigirwamungu-Bargeman M, van der Palen J, van Det MJ, van Meeteren NLU, Klaase JM.

Objective: To assess the effects of a 3-week community-based exercise program on 30-day postoperative complications in high-risk patients scheduled for elective colorectal resection for (pre)malignancy.
Background data: Patients with a low preoperative aerobic fitness undergoing colorectal surgery have an increased risk of postoperative complications. It remains, however, to be demonstrated whether prehabilitation in these patients reduces postoperative complications**.**
Methods: This 2-center, prospective, single-blinded randomized clinical trial was carried out in 2 large teaching hospitals in the Netherlands. Patients (≥60 years) with colorectal (pre)malignancy scheduled for elective colorectal resection and with a score ≤7 metabolic equivalents on the veterans-specific activity questionnaire were randomly assigned to the prehabilitation group or the usual care group by using block-stratified randomization. An oxygen uptake at the ventilatory anaerobic threshold <11 mL/kg/min at the baseline cardiopulmonary exercise test was the final inclusion criterion. Inclusion was based on a power analysis. Patients in the prehabilitation group participated in a personalized 3-week (3 sessions per week, nine sessions in total) supervised exercise program given in community physical therapy practices before colorectal resection. Patients in the reference group received usual care. The primary outcome was the number of patients with one or more complications within 30 days of surgery, graded according to the Clavien-Dindo classification. Data were analyzed on an intention-to-treat basis**.**
Results: Between February 2014 and December 2018, 57 patients [30 males and 27 females; mean age 73.6 years (standard deviation 6.1), range 61-88 years] were randomized to either prehabilitation (n = 28) or usual care (n = 29). The rate of postoperative complications was lower in the prehabilitation group (n = 12, 42.9%) than in the usual care group (n = 21, 72.4%, relative risk 0.59, 95% confidence interval 0.37-0.96, P = 0.024).
Conclusions: Exercise prehabilitation reduced postoperative complications in high-risk patients scheduled to undergo elective colon resection for (pre)malignancy. Prehabilitation should be considered as usual care in high-risk patients scheduled for elective colon, and probably also rectal, surgery.

Gepubliceerd: Ann Surg. 2022;275(2):e299-e306.
Impact factor: 13.787 ; Q1

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2. The association between preoperative body composition and aerobic fitness in patients scheduled for colorectal surgery
Berkel AEM, van Wijk L, van Dijk DPJ, Prins SN, van der Palen J, van Meeteren NLU, Olde Damink SWM, Klaase JM, Bongers BC.

Aim: Although cardiopulmonary exercise testing (CPET) is considered the gold standard, a preoperative abdominal CT scan might also provide information concerning preoperative aerobic fitness for risk assessment. This study aimed to investigate the association between preoperative CT-scan-derived body composition variables and preoperative CPET variables of aerobic fitness in colorectal surgery.
Method: In this retrospective cohort study, CT images at level L3 were analysed for skeletal muscle mass, skeletal muscle radiation attenuation, visceral adipose tissue (VAT) mass and subcutaneous

adipose tissue mass. Regression analyses were performed to investigate the relation between CT-scan-derived body composition variables, CPET-derived aerobic fitness and other preoperative patient-related variables. Logistic regression analysis was performed to predict a preoperative anaerobic threshold (AT) ≤ 11.1 ml/kg/min as cut-off for having a high risk for postoperative complications**.**
Results: Data from 78 patients (45 men; mean [SD] age 74.5 [6.4 years]) were analysed. A correlation coefficient of 0.55 was observed between absolute AT and skeletal muscle mass index. Absolute AT (R(2) of 51.1%) was lower in patients with a lower skeletal muscle mass index, together with higher age, lower body mass and higher American Society of Anesthesiologists (ASA) score. Higher ASA score (odds ratio 5.64; P = 0.033) and higher VAT mass (odds ratio 1.02; P = 0.036) were associated with an increased risk of an AT ≤ 11.1 ml/kg/min**.**
Conclusion: Body composition variables from the preoperative CT scan were moderately associated with preoperative CPET-derived aerobic fitness. Higher ASA score and higher VAT mass were associated with an increased risk of an AT ≤ 11.1 ml/kg/min.

Gepubliceerd: Colorectal Dis. 2022;24(1):93-101.
Impact factor: 3.917; Q3

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3. Factors influencing endoscopic estimation of colon polyp size in a colon model
Beukema KR, Simmering JA, Brusse-Keizer M, John S, Quispel R, Mensink PB.

Background/Aims: Colorectal polyps are removed to prevent progression to colorectal cancer. Polyp size is an important factor for risk stratification of malignant transformation. Endoscopic size estimation correlates poorly with pathological reports and several factors have been suggested to influence size estimation. We aimed to gain insight into the factors influencing endoscopic polyp size estimation**.**
Methods: Images of polyps in an artificial model were obtained at 1, 3, and 5 cm from the colonoscope's tip. Participants were asked to estimate the diameter and volume of each polyp**.**
Results: Fifteen endoscopists from three large-volume centers participated in this study. With an intraclass correlation coefficient of 0.66 (95% confidence interval [CI], 0.62-0.71) for diameter and 0.56 (95% CI, 0.50-0.62) for volume. Polyp size estimated at 3 cm from the colonoscope's tip yielded the best results. A lower distance between the tip and the polyp was associated with a larger estimated polyp size**.**
Conclusion: Correct endoscopic estimation of polyp size remains challenging. This finding can affect size estimation skills and future training programs for endoscopists.

Gepubliceerd: Clin Endosc. 2022;55(4):540-8.
Impact factor: 0 ; Q NVT

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4. Coeliac Artery Release or Sham Operation in Patients Suspected of Having Median Arcuate Ligament Syndrome: The CARoSO study
Blauw JTM, Metz FM, Brusse-Keizer M, Rijnja P, Bruno MJ, Geelkerken RH.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2022;64(5):573-4.
Impact factor: 6.427 ; Q1

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5. Difference in survival between COPD patients with an impaired immune reaction versus an adequate immune reaction to seasonal influenza vaccination: The COMIC study

Brusse-Keizer M, Citgez E, Zuur-Telgen M, Kerstjens HAM, Rijkers G, Van der Valk PDLPM, van der Palen J.

Aim: To study the hypothesis that COPD patients who do not achieve seroprotective levels after influenza vaccination, are a less immune-competent group with a higher risk of morbidity and mortality**.**
Methods: 578 patients included in the COMIC cohort had pre- and post-vaccination stable state blood samples in which influenza-vaccine specific antibodies were measured. Post-vaccination titers of ≥40 were considered protective and indicative of being immuno-competent. Primary outcome was all-cause mortality. Morbidity was defined as time till first severe acute exacerbation in COPD (severe AECOPD) and time till first community acquired pneumonia (CAP)**.**
Results: 42% of the patients achieved seroprotective levels to both H1N1 and H3N2 after vaccination. Seroprotective levels to H3N2 were markedly higher (96%) than to H1N1(43%). Having seroprotective levels to both H1N1 and H3N2 was not associated with less morbidity (severe AECOPD HR 0.91 (95% 0.66-1.25; p = 0.564) (CAP HR 1.23 (95% 0.75-2.00; p = 0.412)) or lower mortality (HR 1.10(95% 0.87-1.38; p = 0.433))**.**
Conclusion: In a large well-characterized COPD cohort only the minority of patients achieved seroprotective titers to H1N1 and H3N1 after the yearly influenza vaccination. While achieving seroprotection after vaccination can be considered a surrogate marker of being immunocompetent, this was not associated with lower morbidity and mortality. Whether this means that the immune status is not a relevant pheno/endotype in COPD patients for the course of their disease or that seroprotection is not an adequate (surrogate) marker to define the immune status in COPD needs to be further studied.

Gepubliceerd: Respir Med. 2022;197:106851.
Impact factor: 4.582 ; Q2

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6. A Host-Directed Approach to the Detection of Infection in Hard-to-Heal Wounds
Burnet M, Metcalf DG, Milo S, Gamerith C, Heinzle A, Sigl E, Eitel K, Haalboom M, Bowler PG.

Wound infection is traditionally defined primarily by visual clinical signs, and secondarily by microbiological analysis of wound samples. However, these approaches have serious limitations in determining wound infection status, particularly in early phases or complex, chronic, hard-to-heal wounds. Early or predictive patient-derived biomarkers of wound infection would enable more timely and appropriate intervention. The observation that immune activation is one of the earliest responses to pathogen activity suggests that immune markers may indicate wound infection earlier and more reliably than by investigating potential pathogens themselves. One of the earliest immune responses is that of the innate immune cells (neutrophils) that are recruited to sites of infection by signals associated with cell damage. During acute infection, the neutrophils produce oxygen radicals and enzymes that either directly or indirectly destroy invading pathogens. These granular enzymes vary with cell type but include elastase, myeloperoxidase, lysozyme, and cathepsin G. Various clinical studies have demonstrated that collectively, these enzymes, are sensitive and reliable markers of both early-onset phases and established infections. The detection of innate immune cell enzymes in hard-to-heal wounds at point of care offers a new, simple, and effective approach to determining wound infection status and may offer significant advantages over uncertainties associated with clinical judgement, and the questionable value of wound microbiology. Additionally, by facilitating the detection of early wound infection, prompt, local wound hygiene interventions will likely enhance infection resolution and wound healing, reduce the requirement for systemic antibiotic therapy, and support antimicrobial stewardship initiatives in wound care.

Gepubliceerd: Diagnostics (Basel). 2022;12(10).
Impact factor: 3.992; Q1

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7. ISARIC-COVID-19 dataset: A Prospective, Standardized, Global Dataset of Patients Hospitalized with COVID-19
Garcia-Gallo E, Merson L, Kennon K, Kelly S, Citarella BW, Fryer DV, Shrapnel S, Lee J, Duque S, Fuentes YV, Balan V, Smith S, Wei J, Gonçalves BP, Russell CD, Sigfrid L, Dagens A, Olliaro PL, Baruch J, Kartsonaki C, Dunning J, Rojek A, Rashan A, Beane A, Murthy S, Reyes LF, ISARIC Clinical Characterization Group: Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H.

The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) COVID-19 dataset is one of the largest international databases of prospectively collected clinical data on people hospitalized with COVID-19. This dataset was compiled during the COVID-19 pandemic by a network of hospitals that collect data using the ISARIC-World Health Organization Clinical Characterization Protocol and data tools. The database includes data from more than 705,000 patients, collected in more than 60 countries and 1,500 centres worldwide. Patient data are available from acute hospital admissions with COVID-19 and outpatient follow-ups. The data include signs and symptoms, pre-existing comorbidities, vital signs, chronic and acute treatments, complications, dates of hospitalization and discharge, mortality, viral strains, vaccination status, and other data. Here, we present the dataset characteristics, explain its architecture and how to gain access, and provide tools to facilitate its use.

Gepubliceerd: Sci Data. 2022;9(1):454.
Impact factor: 8.501 ; Q1

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8. Stepwise model development and simultaneous validation to keep up with clinically relevant and rapidly changing diagnostic techniques
Haalboom M, Kort S, van der Palen J.

Gepubliceerd: J Clin Epidemiol. 2022;142:332.
Impact factor: 7.407 ; Q1

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9. Using a stepwise approach to simultaneously develop and validate machine learning based prediction models
Haalboom M, Kort S, van der Palen J.

Accurate diagnosis of a disease is essential in healthcare. Prediction models, based on classical regression techniques, are widely used in clinical practice. Machine Learning (ML) techniques might be preferred in case of a large amount of data per patient and relatively limited numbers of subjects. However, this increases the risk of overfitting, and external validation is imperative. However, in the field of ML, new and more efficient techniques are developed rapidly, and if recruiting patients for a validation study is time consuming, the ML technique used to develop the first model might have been surpassed by more efficient ML techniques, rendering this original model no longer relevant. We demonstrate a stepwise design for simultaneous development and validation of prediction models based on ML techniques. The design enables - in one study - evaluation of the stability and robustness of a prediction model over increasing sample size as well as assessment of the stability of sensitivity/specificity at a chosen cut-off. This will shorten the time to introduction of a new test in

health care. We finally describe how to use regular clinical parameters in conjunction with ML based predictions, to further enhance differentiation between subjects with and without a disease.

Gepubliceerd: J Clin Epidemiol. 2022;142:305-10.
Impact factor: 7.407 ; Q1

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10. High Titers of Low Affinity Antibodies in COVID-19 Patients Are Associated With Disease Severity
Hendriks J, Schasfoort R, Koerselman M, Dannenberg M, Cornet AD, Beishuizen A, van der Palen J, Krabbe J, Mulder AHL, Karperien M.

Background: Almost 2 years from the beginning of the coronavirus disease 2019 (COVID-19) pandemic, there is still a lot unknown how the humoral response affects disease progression. In this study, we investigated humoral antibody responses against specific SARS-CoV2 proteins, their strength of binding, and their relationship with COVID severity and clinical information. Furthermore, we studied the interactions of the specific receptor-binding domain (RBD) in more depth by characterizing specific antibody response to a peptide library.
Material and Methods: We measured specific antibodies of isotypes IgM, IgG, and IgA, as well as their binding strength against the SARS-CoV2 antigens RBD, NCP, S1, and S1S2 in sera of 76 COVID-19 patients using surface plasmon resonance imaging. In addition, these samples were analyzed using a peptide epitope mapping assay, which consists of a library of peptides originating from the RBD**.**
Results: A positive association was observed between disease severity and IgG antibody titers against all SARS-CoV2 proteins and additionally for IgM and IgA antibodies directed against RBD. Interestingly, in contrast to the titer of antibodies, the binding strength went down with increasing disease severity. Within the critically ill patient group, a positive association with pulmonary embolism, d-dimer, and antibody titers was observed**.**
Conclusion: In critically ill patients, antibody production is high, but affinity is low, and maturation is impaired. This may play a role in disease exacerbation and could be valuable as a prognostic marker for predicting severity.

Gepubliceerd: Front Immunol. 2022;13:867716.
Impact factor: 8.787 ; Q1

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11. Can the response to a single dose of beclomethasone dipropionate predict the outcome of long-term treatment in childhood exercise-induced bronchoconstriction?
Hengeveld VS, Lammers N, van der Kamp MR, van der Palen J, Thio BJ.

Background: Exercise-induced bronchoconstriction (EIB) is a frequent and highly specific symptom of childhood asthma. Inhaled corticosteroids (ICS) are the mainstay of controller therapy for EIB and asthma; however, a proportion of asthmatic children and adolescents is less responsive to ICS. We hypothesized that a single dose response to ICS could function as a predictor for individual long-term efficacy of ICS.
Objective: To assess the predictive value of the bronchoprotective effect of a single-dose beclomethasone dipropionate (BDP) against EIB for the bronchoprotective effect of 4 weeks of treatment, using an exercise challenge test (ECT)**.**
Methods: Thirty-two steroid-naïve children and adolescents aged 6 to 18 years with EIB were included in this prospective cohort study. They performed an ECT at baseline, after a single-dose BDP (200µg) and after 4 weeks of BDP treatment (100 µg twice daily) to assess EIB severity**.**

Results: The response to a single-dose BDP on exercise-induced fall in FEV1 showed a significant correlation with the response on exercise-induced fall in FEV1 after 4 weeks of BDP treatment (r = .38, p = .004). A reduction in post-exercise fall in FEV1 of more than 8% after a single-dose BDP could predict BDP efficacy against EIB after 4 weeks of treatment with a positive predictive value of 100% (CI: 86.1-100%) and a negative predictive value of 29.4% (CI: 11.7%-53.7%)**.**
Conclusion: We found that the individual response to a single-dose BDP against EIB has a predictive value for the efficacy of long-term treatment with BDP. This could support clinicians in providing personalized management of EIB in childhood asthma.

Gepubliceerd: Pediatr Allergy Immunol. 2022;33(6):e13808.
Impact factor: 2.676 ; Q1

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12. The clinical relevance of various methods of classifying ipsilateral breast tumour recurrence as either true local recurrence or new primary
Jobsen JJ, Struikmans H, Siemerink E, van der Palen J, Heijmans HJ.

Purpose: Describes the relevance of -various classification methods for ipsilateral breast tumour recurrence (IBTR) as either true recurrence (TR) or new primary (NP) on both disease-specific survival (DSS) and distant metastasis-free survival (DMFS).
Method: Two hundred and thirty-four of 4359 women undergoing breast-conserving therapy experienced IBTR. We compared the impact of four known classification methods and two newly created classification methods**.**
Results: For three of the methods, a better DSS was observed for NP compared to TR with the hazard ratio (HR) ranging from 0.5 to 0.6. The new Twente method classification, comprising all classification criteria of three known methods, and the new Morphology method, using only morphological criteria, had the best HR and confidence interval with a HR 0.5 (95% CI 0.2-1.0) and a HR 0.5 (95% CI 0.3-1.1), respectively. For DMFS, the HR for NP compared to TR ranged from 0.6 to 0.9 for all six methods. The new Morphology method and the Twente method noted the best HR and confidence intervals with a HR 0.6 (95% CI 0.3-1.1) and a HR 0.6 (95% CI 0.4-1.2), respectively**.**
Conclusion: IBTR classified as TR or NP has a prognostic value for both DSS and DMFS, but depends on the classification method used. Developing and validating a generally accepted form of classification are imperative for using TR and NP in clinical practice.

Gepubliceerd: Breast Cancer Res Treat. 2022;195(3):249-62.
Impact factor: 4.624; Q2

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13. Clinical relevance of the timing of radiotherapy after breast-conserving surgery : Results of a large, single-centre, population-based cohort study
Jobsen JJ, Struikmans H, van der Palen J, Siemerink EJM.

Purpose: To investigate the effect of the timing of radiation therapy after breast-conserving surgery in relation to distant metastasis-free survival and disease-specific survival**.**
Methods: The analysis was performed in relation to 4189 women all undergoing breast-conserving therapy (BCT). Three groups were defined with respect to lymph node status and the use of adjuvant systemic therapy (AST). Patients were categorized into time intervals: < 37 days, 37-53 days, 54-112 days and > 112 days**.**
Results: For women without lymph node metastases and with favourable characteristics aged > 55 years, an improved treatment efficacy was noted when starting radiotherapy with a time interval of < 37 days. The same was observed for women with lymph nodes metastases receiving AST

aged ≤ 50 years. Finally, for women aged > 50 years with negative lymph node status but with unfavourable characteristics and receiving AST, an improved treatment efficacy was noted when starting radiotherapy after a time interval of ≥ 37 days**.**
Conclusion: The results of our study further support the hypothesis that the timing of radiotherapy may have an impact on treatment efficacy and that further studies (preferably randomized trials) are indicated.

Gepubliceerd: Strahlenther Onkol. 2022;198(3):268-81.
Impact factor: 4.033 ; Q2

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14. Limited Impact of Breast Cancer and Non-breast Malignancies on Survival in Older Patients with Early-Stage Breast Cancer: Results of a Large, Single-Centre, Population-Based Study
Jobsen JJ, van der Palen J, Siemerink E, Struikmans H.

Aims: To analyse the disease-free survival and overall survival in older adults with breast cancer after breast-conserving therapy, focusing on the relevance of non-breast malignancy (NBM) with respect to survival rates.
Material and Methods: Analyses were based on 1205 women aged 65 years and older with breast cancer treated with breast-conserving therapy between 1999 and 2015. Patients were divided into three age categories: 65-70, 71-75 and >75 years. Multivariate survival analysis was carried out using Cox regression analysis**.**
Results: The two youngest age categories showed excellent results, with a 12-year disease-free survival of 84.6 and 86.3%, respectively. We noted a 17.2% incidence of NBM, particularly for colon cancer and lung cancer. Most (72.9%) occurred after a diagnosis of breast cancer. Of those 72.9%, about 50% died as a result of NBM within 2 years of the diagnosis of NBM. The overall 12-year NBM-specific survival was 92.0%. The 12-year overall survival was 60.0% for all and for the three abovementioned age categories was 73.3, 54.4 and 28.4%, respectively. The cause of death for all was predominantly non-malignancy-related morbidity**.**
Conclusion: The impact of breast cancer on life expectancy was limited, in particularly for women aged 65-75 years. The relevance of NBM on survival was limited.

Gepubliceerd: Clin Oncol (R Coll Radiol). 2022;34(6):355-62.
Impact factor: 4.925; Q2

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15. Effect of metformin on outcome after acute ischemic stroke in patients with type 2 diabetes mellitus
Kersten C, Knottnerus ILH, Heijmans E, Haalboom M, Zandbergen AAM, den Hertog HM.

Introduction: Diabetes mellitus is a well-known risk factor for ischemic stroke and is associated with unfavorable outcome after stroke. Metformin is recommended as first-line treatment in these patients. Pre-stroke metformin use might have neuroprotective properties resulting in reduced stroke severity. However, results of the effects of pre-stroke metformin use on functional outcome are conflicting and has not been previously described in patients with type 2 diabetes mellitus regardless of stroke severity or revascularization treatment. In this study, we aimed to assess the association between metformin use and functional outcome in patients with type 2 diabetes mellitus and acute ischemic stroke**.**
Methods: We used data from patients with known type 2 diabetes mellitus who were admitted with acute ischemic stroke between 2017 and 2021 in the Isala Hospital Zwolle and Medisch Spectrum Twente (MST) Enschede, the Netherlands. The association between pre-stroke metformin use and

favorable functional outcome at 3 months (defined as modified Rankin Scale (mRS) < 3) was expressed as Odds Ratios (ORs) with corresponding confidence intervals (CIs). Adjustments were made for age, sex, hyperglycemia on admission and revascularization treatment by means of multiple logistic regression**.**
Results: Nine hundred thirty seven patients were included of whom 592 patients (63%) used metformin. Six hundred seventy eight (74%) patients were hyperglycemic on admission. Median mRS was 3 (IQR 2-6) and 593 patients (63%) had a favorable outcome. Pre-stroke metformin use was associated with favorable outcome (aOR of 1.94 (95%- CI 1.45-2.59))**.**
Conclusion: In this study, we showed that pre-stroke metformin use was associated with favorable outcome after acute ischemic stroke in patients with diabetes mellitus type 2.

Gepubliceerd: J Stroke Cerebrovasc Dis. 2022;31(9):106648.
Impact factor: 2.677 ; Q3

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16. Association of hyperglycemia and computed tomographic perfusion deficits in patients who underwent endovascular treatment for acute ischemic stroke caused by a proximal intracranial occlusion: A subgroup analysis of a randomized phase 3 trial (MR CLEAN)
Kersten C, Zandbergen AAM, Berkhemer OA, Borst J, Haalboom M, Roos Y, Dippel DWJ, van Oostenbrugge RJ, van der Lugt A, van Zwam WH, Majoie CB, den Hertog HM.

Introduction: Hyperglycemia is highly prevalent in patients with acute ischemic stroke and is associated with increased risk of symptomatic intracranial hemorrhage, larger infarct size and unfavorable outcome. Furthermore, glucose may modify the effect of endovascular treatment (EVT) in patients with ischemic stroke. Hyperglycemia might lead to accelerated conversion of penumbra into infarct core. However, it remains uncertain whether hyperglycemia on admission is associated with the size of penumbra or infarct core in acute ischemic stroke. In this study, we aimed to assess the association between hyperglycemia and Computed Tomographic Perfusion (CTP) derived parameters in patients who underwent EVT for acute ischemic stroke**.**
Methods: We used data from the MR CLEAN study (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands). Hyperglycemia was defined as admission serum glucose of >7.8 mmol/L. Dichotomized and quantiles of glucose levels were related to size of core, penumbra and core penumbra ratio. Hypoperfused area is mean transient time 45% higher than that of the contralateral hemisphere. Core is the area with cerebral blood volume of <2 mL/100 g and penumbra is the area with cerebral blood volume > 2 mL/100 g. Core-penumbra ratio is the ischemic core divided by the total volume of hypoperfused tissue (core plus penumbra) multiplied by 100. Adjustments were made for age, sex, NIHSS on admission, onset-imaging time and diabetes mellitus**.**
Results: Hundred seventy-three patients were included. Median glucose level on admission was 6.5 mmol/L (IQR 5.8-7.5 mmol/L) and thirty-five patients (20%) were hyperglycemic. Median core volume was 33.3 mL (IQR 13.6-62.4 mL), median penumbra volume was 80.2 mL (IQR 36.3-123.5 mL) and median core-penumbra ratio was 28.5% (IQR 18.6-45.8%). Patients with hyperglycemia on admission had larger core volumes and core penumbra ratio than normoglycemic patients with a regression coefficient of 15.1 (95% confidence interval (CI), 1.8 to 28.3) and 11.5 (95% confidence interval (CI), 3.4 to 19.7) respectively**.**
Conclusion: Hyperglycemia on admission was associated with larger ischemic core volume and larger core-penumbra ratio in patients with acute ischemic stroke who underwent endovascular treatment.

Gepubliceerd: J Neurol Sci. 2022;440:120333.
Impact factor: 4.553 ; Q2

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17. Reliability assessment of hyperspectral imaging with the HyperView™ system for lower extremity superficial tissue oxygenation in young healthy volunteers
Kleiss SF, Ma KF, El Moumni M, Schuurmann RCL, Zeebregts CJ, Haalboom M, Bokkers RPH, de Vries JPM.

Purpose: Hyperspectral imaging (HSI) is a noninvasive spectroscopy technique for determining superficial tissue oxygenation. The HyperView™ system is a hand-held camera that enables perfusion image acquisition. The evaluation of superficial tissue oxygenation is warranted in the evaluation of patients with peripheral arterial disease. The aim was to determine the reliability of repeated HSI measurements**.**
Methods: In this prospective cohort study, HSI was performed on 50 healthy volunteers with a mean age of 26.4 ± 2.5 years, at the lower extremity. Two independent observers performed HSI during two subsequent measurement sessions. Short term test-retest reliability and intra- and inter-observer reliability were determined, and generalizability and decision studies were performed. Transcutaneous oxygen pressure (TcPO(2)) measurements were also performed**.**
Results: The short term test-retest reliability was good for the HSI values determined at the lower extremity, ranging from 0.72 to 0.90. Intra- and inter-observer reliability determined at different days were poor to moderate for both HSI (0.24 to 0.71 and 0.30 to 0.58, respectively) and TcPO(2) (0.54 and 0.56, and 0.51 and 0.31, respectively). Reliability can be increased to >0.75 by averaging two measurements on different days**.**
Conclusion: This study showed good short term test-retest reliability for HSI measurements, however low intra- and inter-observer reliability was observed for tissue oxygenation measurements with both HSI and TcPO(2) performed at separate days in young healthy volunteers. Reliability of HSI can be improved when determined as a mean of two measurements taken on different days.

Gepubliceerd: J Clin Monit Comput. 2022;36(3):713-23.
Impact factor: 1.977 ; Q4

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18. Effect of physical exercise on the hippocampus and global grey matter volume in breast cancer patients: A randomized controlled trial (PAM study)
Koevoets EW, Geerlings MI, Monninkhof EM, Mandl R, Witlox L, van der Wall E, Stuiver MM, Sonke GS, Velthuis MJ, Jobsen JJ, van der Palen J, Bos M, Göker E, Menke-Pluijmers MBE, Sommeijer DW, May AM, de Ruiter MB, Schagen SB.

Background: Physical exercise in cancer patients is a promising intervention to improve cognition and increase brain volume, including hippocampal volume. We investigated whether a 6-month exercise intervention primarily impacts total hippocampal volume and additionally hippocampal subfield volumes, cortical thickness and grey matter volume in previously physically inactive breast cancer patients. Furthermore, we evaluated associations with verbal memory**.**
Methods: Chemotherapy-exposed breast cancer patients (stage I-III, 2-4 years post diagnosis) with cognitive problems were included and randomized in an exercise intervention (n = 70, age = 52.5 ± 9.0 years) or control group (n = 72, age = 53.2 ± 8.6 years). The intervention consisted of 2x1 hours/week of supervised aerobic and strength training and 2x1 hours/week Nordic or power walking. At baseline and at 6-month follow-up, volumetric brain measures were derived from 3D T1-weighted 3T magnetic resonance imaging scans, including hippocampal (subfield) volume (FreeSurfer), cortical thickness (CAT12), and grey matter volume (voxel-based morphometry CAT12). Physical fitness was measured with a cardiopulmonary exercise test. Memory functioning was measured with the Hopkins Verbal Learning Test-Revised (HVLT-R total recall) and Wordlist Learning of an online cognitive test battery, the Amsterdam Cognition Scan (ACS Wordlist Learning). An

explorative analysis was conducted in highly fatigued patients (score of ≥ 39 on the symptom scale 'fatigue' of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire), as previous research in this dataset has shown that the intervention improved cognition only in these patients.
Results: Multiple regression analyses and voxel-based morphometry revealed no significant intervention effects on brain volume, although at baseline increased physical fitness was significantly related to larger brain volume (e.g., total hippocampal volume: R = 0.32, B = 21.7 mm(3), 95 % CI = 3.0 - 40.4). Subgroup analyses showed an intervention effect in highly fatigued patients. Unexpectedly, these patients had significant reductions in hippocampal volume, compared to the control group (e.g., total hippocampal volume: B = -52.3 mm(3), 95 % CI = -100.3 - -4.4)), which was related to improved memory functioning (HVLT-R total recall: B = -0.022, 95 % CI = -0.039 - -0.005; ACS Wordlist Learning: B = -0.039, 95 % CI = -0.062 - -0.015).
Conclusions: No exercise intervention effects were found on hippocampal volume, hippocampal subfield volumes, cortical thickness or grey matter volume for the entire intervention group. Contrary to what we expected, in highly fatigued patients a reduction in hippocampal volume was found after the intervention, which was related to improved memory functioning. These results suggest that physical fitness may benefit cognition in specific groups and stress the importance of further research into the biological basis of this finding.

Gepubliceerd: Neuroimage Clin. 2022;37:103292.
Impact factor: 4.891 ; Q2

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19. Effect of physical exercise on cognitive function after chemotherapy in patients with breast cancer: a randomized controlled trial (PAM study)
Koevoets EW, Schagen SB, de Ruiter MB, Geerlings MI, Witlox L, van der Wall E, Stuiver MM, Sonke GS, Velthuis MJ, Jobsen JJ, Menke-Pluijmers MBE, Göker E, van der Pol CC, Bos M, Tick LW, van Holsteijn NA, van der Palen J, May AM, Monninkhof EM.

Background: Up to 60% of breast cancer patients treated with chemotherapy is confronted with cognitive problems, which can have a significant impact on daily activities and quality of life (QoL). We investigated whether exercise training improves cognition in chemotherapy-exposed breast cancer patients 2-4 years after diagnosis.
Methods: Chemotherapy-exposed breast cancer patients, with both self-reported cognitive problems and lower than expected performance on neuropsychological tests, were randomized to an exercise or control group. The 6-month exercise intervention consisted of supervised aerobic and strength training (2 h/week), and Nordic/power walking (2 h/week). Our primary outcome was memory functioning (Hopkins Verbal Learning Test-Revised; HVLT-R). Secondary outcomes included online neuropsychological tests (Amsterdam Cognition Scan; ACS), self-reported cognition (MD Anderson Symptom Inventory for multiple myeloma; MDASI-MM), physical fitness (relative maximum oxygen uptake; VO(2peak)), fatigue (Multidimensional Fatigue Inventory), QoL (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ C-30), depression (Patient Health Questionnaire-9, Hospital Anxiety and Depression Scale; HADS), and anxiety (HADS). HVLT-R total recall was analyzed with a Fisher exact test for clinically relevant improvement (≥ 5 words). Other outcomes were analyzed using multiple regression analyses adjusted for baseline and stratification factors.
Results: We randomized 181 patients to the exercise (n = 91) or control group (n = 90). Two-third of the patients attended ≥ 80% of the exercise sessions, and physical fitness significantly improved compared to control patients (B VO(2peak) 1.4 ml/min/kg, 95%CI:0.6;2.2). No difference in favor of the intervention group was seen on the primary outcome. Significant beneficial intervention effects were found for self-reported cognitive functioning [MDASI-MM severity (B-0.7, 95% CI - 1.2; - 0.1)],

fatigue, QoL, and depression. A hypothesis-driven analysis in highly fatigued patients showed positive exercise effects on tested cognitive functioning [ACS Reaction Time (B-26.8, 95% CI - 52.9; - 0.6) and ACS Wordlist Learning (B4.4, 95% CI 0.5; 8.3)].
Conclusions: A 6-month exercise intervention improved self-reported cognitive functioning, physical fitness, fatigue, QoL, and depression in chemotherapy-exposed breast cancer patients with cognitive problems. Tested cognitive functioning was not affected. However, subgroup analysis indicated a positive effect of exercise on tested cognitive functioning in highly fatigued patients. Trial Registration Netherlands Trial Registry: Trial NL5924 (NTR6104). Registered 24 October 2016, https://www.trialregister.nl/trial/5924 .

Gepubliceerd: Breast Cancer Res. 2022;24(1):36.
Impact factor: 8.408; Q1

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20. Non-cardiovascular medication and readmission for heart failure: an observational cohort study
Kruik-Kollöffel WJ, Vallejo-Yagüe E, Movig KLL, Linssen GCM, Heintjes EM, van der Palen J.

Background: Among heart failure (HF) patients, hospital readmissions are a major concern. The medication taken by a patient may provide information on comorbidities and conditions and may be used as an indicator to identify populations at an increased risk of HF readmission. Aim This study explored the use of non-cardiovascular medication at hospital discharge from the first HF admission in search of indicators of high risk of readmission for HF. Method The study included 22,476 HF patients from the Dutch PHARMO Database Network at their first HF hospitalization. The data was divided into training and validation sets. A Cox regression model with demographics, date of first HF hospital admission and non-cardiovascular medication present at discharge, adjusted for cardiovascular medication, was developed in the training set and subsequently implemented in the validation set. Results The study included 22,476 patients, mean age 76.7 years (range 18-104) and median follow-up time 2.5 years (range 0-15.7 years). During the study period 6,725 (29.9%) patients were readmitted for HF, with a median time-to-readmission of 7 months (range 0-14.3 years). Non-cardiovascular medication associated with a high risk of readmission for HF were identified as indicators of high risk, with no implied causal relationship. Patients prescribed antigout medications presented a 25% increased risk of readmission (HR 1.25, 95%CI 1.09-1.45, P = 0.002). Patients using insulin had an 18% higher risk of readmission versus patients not using insulin (HR 1.18, 95%CI 1.06-1.32, P = 0.002), but not versus patients treated with other blood-glucose-lowering drugs. No association between the risk of readmission and NSAIDs use was observed. Conclusion The results suggest that diabetes is responsible for the higher HF-readmission risk observed in patients prescribed insulin. The observed risk in users of antigout medication should be further investigated. The absence of an association with the use of NSAIDs should be interpreted with caution.

Gepubliceerd: Int J Clin Pharm. 2022;44(3):762-8.
Impact factor: 2.305 ; Q4

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21. Patient and Health Care Provider Perspectives on Potential Preventability of Hospital Admission for Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Qualitative Study
Leenders A, Sportel E, Poppink E, van Beurden W, van der Valk P, Brusse-Keizer M.

Purpose: Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic disease partly characterised by the occurrence of acute exacerbations (AECOPD). The need for hospital admissions for COPD exacerbations could theoretically be decreased through timely and appropriate outpatient

care or self-management. The aim of this study is to explore and compare patients' and health care providers' (HCP) perspectives on the potential preventability of COPD hospitalisations and to identify strategies to prevent unnecessary hospitalisations.
Patients and Methods: Semi-structured interviews were conducted with patients admitted for an AECOPD (N = 11), HCPs on the respiratory ward (N = 11), and treating pulmonologists (N = 10). Interviews were transcribed verbatim and analysed using thematic content analysis**.**
Results: Patient and HCP perspectives on the potential preventability of hospital admissions for AECOPD often conflict. The kappa coefficients were -0.18 [95% CI: -0.46-0.11] for patients and pulmonologists and -0.28 [95% CI: -0.80-0.21] for patients and HCPs, which indicates poor agreement. The kappa coefficient for pulmonologists and HCPs was 0.14 [95% CI: -0.13-0.41], which indicates slight agreement. Patient and HCP factors that could potentially prevent hospitalisation for AECOPD were identified, including timely calling for help, recognizing and acting on symptoms, and receiving instruction about COPD, including treatment and action plans**.**
Conclusion: Patients and their HCPs have different beliefs about the potential preventability of AECOPD hospitalisations. Most patients and HCPs mentioned factors that potentially could have led to a different outcome for the current AECOPD or that could impact the patient's health status and treatment of AECOPDs in the future. The factors identified in this study indicate that shared decision making is crucial to center the patient's perspective and individual needs and to provide timely treatment or prevention of AECOPD, thereby potentially decreasing hospital admission rates.

Gepubliceerd: Patient Prefer Adherence. 2022;16:3207-20.
Impact factor: 2.314 ; Q3

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22. Systematic Review of the Efficacy of Treatment for Median Arcuate Ligament Syndrome
Metz FM, Blauw JTM, Brusse-Keizer M, Kolkman JJ, Bruno MJ, Geelkerken RH.

Objective: Since the first description of the median arcuate ligament syndrome (MALS), the existence for the syndrome and the efficacy of treatment for it have been questioned**.**
Methods: A systematic review conforming to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement was conducted, with a broader view on treatment for MALS including any kind of coeliac artery release, coeliac plexus resection, and coeliac plexus blockage, irrespective of age. Online databases were used to identify papers published between 1963 and July 2021. The inclusion criteria were abdominal symptoms, proof of MALS on imaging, and articles reporting at least three patients. Primary outcomes were symptom relief and quality of life (QoL)**.**
Results: Thirty-eight studies describing 880 adult patients and six studies describing 195 paediatric patients were included. The majority of the adult studies reported symptom relief of more than 70% from three to 228 months after treatment. Two adult studies showed an improved QoL after treatment. Half of the paediatric studies reported symptom relief of more than 70% from six to 62 months after laparoscopic coeliac artery release, and four studies reported an improved QoL. Thirty-five (92%) adult studies and five (83%) paediatric studies scored a high or unclear risk of bias for the majority of the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) items. The meaning of coeliac plexus resection or blockage could not be substantiated**.**
Conclusion: This systematic review suggests a sustainable symptom relief of more than 70% after treatment for MALS in the majority of adult and paediatric studies; however, owing to the heterogeneity of the inclusion criteria and outcome parameters, the risk of bias was high and a formal meta-analysis could not be performed. To improve care for patients with MALS the next steps would be to deal with reporting standards, outcome definitions, and consensus descriptions of the intervention(s), after which an appropriate randomised controlled trial should be performed.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2022;64(6):720-32.

Impact factor: 6.427 ; Q1

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23. The Effect of a Structured Medication Review on Quality of Life in Parkinson's Disease
Oonk NGM, Movig KLL, van der Palen J, Nibourg SAF, Koehorst-Ter Huurne K, Nijmeijer HW, van Kesteren ME, Dorresteijn LDA.

Background: Drug therapy is important for controlling symptoms in Parkinson's disease (PD). However, it often results in complex medication regimens and could easily lead to drug related problems (DRP), suboptimal adherence and reduced treatment efficacy. A structured medication review (SMR) could address these issues and optimize therapy, although little is known about clinical effects in PD patients.
Objective: To analyze whether an SMR improves quality of life (QoL) in PD**.**
Methods: In this multicenter randomized controlled trial, half of the 202 PD patients with polypharmacy received a community pharmacist-led SMR. The control group received usual care. Assessments at baseline, and after three and six months comprised six validated questionnaires. Primary outcome was PD specific QoL [(PDQ-39; range 0 (best QoL) - 100 (worst QoL)]. Secondary outcomes were disability score, non-motor symptoms, general health status, and personal care giver's QoL. Furthermore, DRPs, proposed interventions, and implemented modifications in medication schedules were analyzed**.**
Results: No improvement in QoL was seen six months after an SMR, with a non-significant treatment effect difference of 2.09 (-0.63;4.80) in favor of the control group. No differences were found in secondary outcomes. In total, 260 potential DRPs were identified (2.6 (±1.8) per patient), of which 62% led to drug therapy optimization**.**
Conclusion: In the current setting, a community pharmacist-led SMR did not improve QoL in PD patients, nor improved other pre-specified outcomes.

Gepubliceerd: J Parkinsons Dis. 2022;12(4):1295-306.
Impact factor: 5.520 ; Q2

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24. Economic Evaluation of the Dr. Bart Application in Individuals With Knee and/or Hip Osteoarthritis
Pelle T, Bevers K, van den Hoogen F, van der Palen J, van den Ende C.

Objective: To evaluate the cost-utility and cost-effectiveness of the dr. Bart app compared to usual care in people with osteoarthritis (OA) of the knees and hips, applying a health care payer perspective**.**
Methods: This economic evaluation was conducted alongside a 6-month randomized controlled trial that included 427 participants. The dr. Bart app is a stand-alone eHealth application that invites users to select pre-formulated goals (i.e., "tiny habits") and triggers for a healthier lifestyle. Self-reported outcome measures were health care costs, quality-adjusted life years (QALYs) according to the EuroQol 5-dimension 3-level (EQ-5D-3L) descriptive system, the EuroQol visual analog scale (QALY VAS), patient activation measure 13 (PAM-13), and 5 subscales of the Knee Injury and Osteoarthritis Outcome Score/Hip Disability and Osteoarthritis Outcome Score. Missing data were multiply imputed, and bootstrapping was used to estimate statistical uncertainty**.**
Results: The mean ± SD age of the study participants was 62.1 ± 7.3 years, and the majority of participants were female (72%). Health care costs were lower in the intervention group compared to the group who received usual care (€-22 [95% confidence interval €-36, -3]). For QALY and QALY VAS, the probability of the dr. Bart app being cost-effective compared to usual care was 0.71 and 0.67, respectively, at a willingness-to-pay (WTP) of €10,000 and 0.64 and 0.56, respectively, at a WTP of

€80.000. For self-management behavior, symptoms, pain, and activities of daily living, the probability that the dr. Bart app was cost-effective was >0.82, and the probability that the dr. Bart app was cost-effective in the areas of activities and quality of life was <0.40, regardless of WTP thresholds**.**
Conclusion: This economic evaluation showed that costs were lower for the dr. Bart app group compared to the group who received usual care. Given the noninvasive nature of the intervention and the moderate probability of it being cost-effective for the majority of outcomes, the dr. Bart app has the potential to serve as a tool to provide education and goal setting in OA and its treatment options.

Gepubliceerd: Arthritis Care Res (Hoboken). 2022;74(6):945-54.
Impact factor: 1.811 ; Q2

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25. Respiratory support in patients with severe COVID-19 in the International Severe Acute Respiratory and Emerging Infection (ISARIC) COVID-19 study: a prospective, multinational, observational study
Reyes LF, Murthy S, Garcia-Gallo E, Merson L, Ibáñez-Prada ED, Rello J, Fuentes YV, Martin-Loeches I, Bozza F, Duque S, Taccone FS, Fowler RA, Kartsonaki C, Gonçalves BP, Citarella BW, Aryal D, Burhan E, Cummings MJ, Delmas C, Diaz R, Figueiredo-Mello C, Hashmi M, Panda PK, Jiménez MP, Rincon DFB, Thomson D, Nichol A, Marshall JC, Olliaro PL, ISARIC Characterization Group: Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H..

Background: Up to 30% of hospitalised patients with COVID-19 require advanced respiratory support, including high-flow nasal cannulas (HFNC), non-invasive mechanical ventilation (NIV), or invasive mechanical ventilation (IMV). We aimed to describe the clinical characteristics, outcomes and risk factors for failing non-invasive respiratory support in patients treated with severe COVID-19 during the first two years of the pandemic in high-income countries (HICs) and low middle-income countries (LMICs)**.**
Methods: This is a multinational, multicentre, prospective cohort study embedded in the ISARIC-WHO COVID-19 Clinical Characterisation Protocol. Patients with laboratory-confirmed SARS-CoV-2 infection who required hospital admission were recruited prospectively. Patients treated with HFNC, NIV, or IMV within the first 24 h of hospital admission were included in this study. Descriptive statistics, random forest, and logistic regression analyses were used to describe clinical characteristics and compare clinical outcomes among patients treated with the different types of advanced respiratory support**.**
Results: A total of 66,565 patients were included in this study. Overall, 82.6% of patients were treated in HIC, and 40.6% were admitted to the hospital during the first pandemic wave. During the first 24 h after hospital admission, patients in HICs were more frequently treated with HFNC (48.0%), followed by NIV (38.6%) and IMV (13.4%). In contrast, patients admitted in lower- and middle-income countries (LMICs) were less frequently treated with HFNC (16.1%) and the majority received IMV (59.1%). The failure rate of non-invasive respiratory support (i.e. HFNC or NIV) was 15.5%, of which 71.2% were from HIC and 28.8% from LMIC. The variables most strongly associated with non-invasive ventilation failure, defined as progression to IMV, were high leukocyte counts at hospital admission (OR [95%CI]; 5.86 [4.83-7.10]), treatment in an LMIC (OR [95%CI]; 2.04 [1.97-2.11]), and tachypnoea at hospital admission (OR [95%CI]; 1.16 [1.14-1.18]). Patients who failed HFNC/NIV had a higher 28-day fatality ratio (OR [95%CI]; 1.27 [1.25-1.30]).
Conclusions: In the present international cohort, the most frequently used advanced respiratory support was the HFNC. However, IMV was used more often in LMIC. Higher leucocyte count, tachypnoea, and treatment in LMIC were risk factors for HFNC/NIV failure. HFNC/NIV failure was related to worse clinical outcomes, such as 28-day mortality. Trial registration This is a prospective

observational study; therefore, no health care interventions were applied to participants, and trial registration is not applicable.

Gepubliceerd: Crit Care. 2022;26(1):276.
Impact factor: 19.344; Q1

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26. "It Really Is an Elusive Illness"-Post-COVID-19 Illness Perceptions and Recovery Strategies: A Thematic Analysis
Schaap G, Wensink M, Doggen CJM, van der Palen J, Vonkeman HE, Bode C.

A substantial number of patients report persisting symptoms after a COVID-19 infection: so-called post-COVID-19 syndrome. There is limited research on patients' perspectives on post-COVID-19 symptoms and ways to recover. This qualitative study explored the illness perceptions and recovery strategies of patients who had been hospitalised for COVID-19. Differences between recovered and non-recovered patients were investigated. Semi-structured in-depth interviews were held with 24 participating patients (8 recovered and 16 non-recovered) 7 to 12 months after hospital discharge. Data were interpreted using reflexive thematic analysis. Four overarching themes were identified: (I) symptoms after hospital discharge; (II) impact of COVID-19 on daily life and self-identity; (III) uncertainty about COVID-19; and (IV) dealing with COVID-19. Formerly hospitalised post-COVID-19 patients seem to have difficulties with making sense of their illness and gaining control over their recovery. The majority of non-recovered participants continue to suffer mostly from weakness or fatigue, dyspnoea and cognitive dysfunction. No notable differences in illness beliefs were observed between recovered and non-recovered participants.

Gepubliceerd: Int J Environ Res Public Health. 2022;19(20).
Impact factor: 4.614 ; Q1

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27. Detection of differentiated thyroid carcinoma in exhaled breath with an electronic nose
Scheepers M, Al-Difaie ZJJ, Wintjens A, Engelen SME, Havekes B, Lubbers T, Coolsen MME, van der Palen J, van Ginhoven TM, Vriens M, Bouvy ND.

This proof-of-principle study investigates the diagnostic performance of the Aeonose in differentiating malignant from benign thyroid diseases based on volatile organic compound analysis in exhaled breath. All patients with a suspicious thyroid nodule planned for surgery, exhaled in the Aeonose. Definitive diagnosis was provided by histopathological determination after surgical resection. Breath samples were analyzed utilizing artificial neural networking. About 133 participants were included, 48 of whom were diagnosed with well-differentiated thyroid cancer. A sensitivity of 0.73 and a negative predictive value (NPV) of 0.82 were found. The sensitivity and NPV improved to 0.94 and 0.95 respectively after adding clinical variables via multivariate logistic regression analysis. This study demonstrates the feasibility of the Aeonose to discriminate between malignant and benign thyroid disease. With a high NPV, low cost, and non-invasive nature, the Aeonose may be a promising diagnostic tool in the detection of thyroid cancer.

Gepubliceerd: J Breath Res. 2022;16(3).
Impact factor: 4.538 ; Q2

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28. Self-management interventions for people with chronic obstructive pulmonary disease
Schrijver J, Lenferink A, Brusse-Keizer M, Zwerink M, van der Valk PD, van der Palen J, Effing TW.

Background: Self-management interventions help people with chronic obstructive pulmonary disease (COPD) to acquire and practise the skills they need to carry out disease-specific medical regimens, guide changes in health behaviour and provide emotional support to enable them to control their disease. Since the 2014 update of this review, several studies have been published.
Objectives: Primary objectives To evaluate the effectiveness of COPD self-management interventions compared to usual care in terms of health-related quality of life (HRQoL) and respiratory-related hospital admissions. To evaluate the safety of COPD self-management interventions compared to usual care in terms of respiratory-related mortality and all-cause mortality. Secondary objectives To evaluate the effectiveness of COPD self-management interventions compared to usual care in terms of other health outcomes and healthcare utilisation. To evaluate effective characteristics of COPD self-management interventions.
Search methods: We searched the Cochrane Airways Trials Register, CENTRAL, MEDLINE, EMBASE, trials registries and the reference lists of included studies up until January 2020.
Selection criteria: Randomised controlled trials (RCTs) and cluster-randomised trials (CRTs) published since 1995. To be eligible for inclusion, self-management interventions had to include at least two intervention components and include an iterative process between participant and healthcare provider(s) in which goals were formulated and feedback was given on self-management actions by the participant.
Data collection and analysis: Two review authors independently selected studies for inclusion, assessed trial quality and extracted data. We resolved disagreements by reaching consensus or by involving a third review author. We contacted study authors to obtain additional information and missing outcome data where possible. Primary outcomes were health-related quality of life (HRQoL), number of respiratory-related hospital admissions, respiratory-related mortality, and all-cause mortality. When appropriate, we pooled study results using random-effects modelling meta-analyses. MAIN RESULTS: We included 27 studies involving 6008 participants with COPD. The follow-up time ranged from two-and-a-half to 24 months and the content of the interventions was diverse. Participants' mean age ranged from 57 to 74 years, and the proportion of male participants ranged from 33% to 98%. The post-bronchodilator forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio of participants ranged from 33.6% to 57.0%. The FEV1/FVC ratio is a measure used to diagnose COPD and to determine the severity of the disease. Studies were conducted on four different continents (Europe (n = 15), North America (n = 8), Asia (n = 1), and Oceania (n = 4); with one study conducted in both Europe and Oceania). Self-management interventions likely improve HRQoL, as measured by the St. George's Respiratory Questionnaire (SGRQ) total score (lower score represents better HRQoL) with a mean difference (MD) from usual care of -2.86 points (95% confidence interval (CI) -4.87 to -0.85; 14 studies, 2778 participants; low-quality evidence). The pooled MD of -2.86 did not reach the SGRQ minimal clinically important difference (MCID) of four points. Self-management intervention participants were also at a slightly lower risk for at least one respiratory-related hospital admission (odds ratio (OR) 0.75, 95% CI 0.57 to 0.98; 15 studies, 3263 participants; very low-quality evidence). The number needed to treat to prevent one respiratory-related hospital admission over a mean of 9.75 months' follow-up was 15 (95% CI 8 to 399) for participants with high baseline risk and 26 (95% CI 15 to 677) for participants with low baseline risk. No differences were observed in respiratory-related mortality (risk difference (RD) 0.01, 95% CI -0.02 to 0.04; 8 studies, 1572 participants ; low-quality evidence) and all-cause mortality (RD -0.01, 95% CI -0.03 to 0.01; 24 studies, 5719 participants; low-quality evidence). We graded the evidence to be of 'moderate' to 'very low' quality according to GRADE. All studies had a substantial risk of bias, because of lack of blinding of participants and personnel to the interventions, which is inherently impossible in a self-management intervention. In addition, risk of bias was noticeably increased because of insufficient information regarding a) non-protocol interventions, and b) analyses to estimate the effect of adhering to interventions. Consequently, the highest GRADE evidence score that could be obtained by studies was 'moderate'.

Conclusions: Self-management interventions for people with COPD are associated with improvements in HRQoL, as measured with the SGRQ, and a lower probability of respiratory-related hospital admissions. No excess respiratory-related and all-cause mortality risks were observed, which strengthens the view that COPD self-management interventions are unlikely to cause harm. By using stricter inclusion criteria, we decreased heterogeneity in studies, but also reduced the number of included studies and therefore our capacity to conduct subgroup analyses. Data were therefore still insufficient to reach clear conclusions about effective (intervention) characteristics of COPD self-management interventions. As tailoring of COPD self-management interventions to individuals is desirable, heterogeneity is and will likely remain present in self-management interventions. For future studies, we would urge using only COPD self-management interventions that include iterative interactions between participants and healthcare professionals who are competent using behavioural change techniques (BCTs) to elicit participants' motivation, confidence and competence to positively adapt their health behaviour(s) and develop skills to better manage their disease. In addition, to inform further subgroup and meta-regression analyses and to provide stronger conclusions regarding effective COPD self-management interventions, there is a need for more homogeneity in outcome measures. More attention should be paid to behavioural outcome measures and to providing more detailed, uniform and transparently reported data on self-management intervention components and BCTs. Assessment of outcomes over the long term is also recommended to capture changes in people's behaviour. Finally, information regarding non-protocol interventions as well as analyses to estimate the effect of adhering to interventions should be included to increase the quality of evidence.

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Impact factor: 11.874; Q1

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29. Impaired Visual Emotion Recognition After Minor Ischemic Stroke
Smith-Spijkerboer W, Meeske K, van der Palen JAM, den Hertog HM, Smeets-Schouten AS, van Hout M, Dorresteijn LDA.

Objective: To assess the prevalence of impaired visual emotion recognition in patients who have experienced a minor ischemic stroke in the subacute phase and to determine associated factors of impaired visual emotion recognition.
Design:A prospective observational study. SETTING: Stroke unit of a teaching hospital. PARTICIPANTS: Patients with minor ischemic stroke (N=112)**.**
Interventions: Not applicable. MAIN OUTCOME MEASURES: Patients with minor stroke underwent a neuropsychological assessment in the subacute phase for visual emotion recognition by the Ekman 60 Faces Test and for general cognition. Univariable linear regression analyses were performed to identify associated factors of emotion recognition impairment**.**
Results: In 112 minor stroke patients, we found a prevalence of 25% of impaired visual emotion recognition. This was significantly correlated with impaired general cognition. Nevertheless, 10.9% of patients with normal general cognition still had impaired emotion recognition. Mood was negatively associated. Stroke localization, hemisphere side, and sex were not associated**.**
Conclusion: Impaired visual emotion recognition is found in about one-quarter of patients with minor ischemic stroke.

Gepubliceerd: Arch Phys Med Rehabil. 2022;103(5):958-63.
Impact factor: 4.060 ; Q1

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30. Therapeutic Alliance in Web-Based Treatment for Eating Disorders: Secondary Analysis of a Randomized Controlled Trial
Stoeten C, de Haan HA, Postel MG, Brusse-Keizer M, Ter Huurne ED.

Background: In face-to-face therapy for eating disorders, therapeutic alliance (TA) is an important predictor of symptom reduction and treatment completion. To date, however, little is known about TA during web-based cognitive behavioral therapy (web-CBT) and its association with symptom reduction, treatment completion, and the perspectives of patients versus therapists.
Objective: This study aimed to investigate TA ratings measured at interim and after treatment, separately for patients and therapists; the degree of agreement between therapists and patients (treatment completers and noncompleters) for TA ratings; and associations between patient and therapist TA ratings and both eating disorder pathology and treatment completion**.**
Methods: A secondary analysis was performed on randomized controlled trial data of a web-CBT intervention for eating disorders. Participants were 170 females with bulimia nervosa (n=33), binge eating disorder (n=68), or eating disorder not otherwise specified (n=69); the mean age was 39.6 (SD 11.5) years. TA was operationalized using the Helping Alliance Questionnaire (HAQ). Paired t tests were conducted to assess the change in TA from interim to after treatment. Intraclass correlations were calculated to determine cross-informant agreement with regard to HAQ scores between patients and therapists. A total of 2 stepwise regressive procedures (at interim and after treatment) were used to examine which HAQ scores predicted eating disorder pathology and therapy completion**.**
Results: For treatment completers (128/170, 75.3%), the HAQ-total scores and HAQ-Helpfulness scores for both patients and therapists improved significantly from interim to post treatment. For noncompleters (42/170, 24.7%), all HAQ scores decreased significantly. For all HAQ scales, the agreement between patients and therapists was poor. However, the agreement was slightly better after treatment than at interim. Higher patient scores on the helpfulness subscale of the HAQ at interim and after treatment were associated with less eating disorder psychopathology. A positive association was found between the HAQ-total patient scores at interim and treatment completion. Finally, posttreatment HAQ-total patient scores and posttreatment HAQ-Helpfulness scores of therapists were positively associated with treatment completion.
Conclusions: Our study showed that TA in web-CBT is predictive of eating disorder pathology and treatment completion. Of particular importance is patients' confidence in their abilities as measured with the HAQ-Helpfulness subscale when predicting posttreatment eating disorder pathology and treatment completion.

Gepubliceerd: JMIR Form Res. 2022;6(6):e33813.
Impact factor: 0 ; Q NVT

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31. A randomized, cross-over study comparing critical and overall errors, learning time, and preference of the ELLIPTA versus BREEZHALER dry powder inhalers in patients with asthma
van der Palen J, Slade D, Rehal S, Verma M, Plank M.

Background: Many patients with asthma make errors using inhalers, affecting the amount of medication received. Previous evidence demonstrated that patients with asthma or chronic obstructive pulmonary disease make fewer critical errors with the ELLIPTA inhaler after reading the patient information leaflet (PIL) versus other dry powder inhalers. We assessed errors made by patients with asthma using placebo ELLIPTA or BREEZHALER inhalers**.**
Methods: This randomized, multicenter, open-label placebo inhaler-handling study (ClinicalTrials.gov: NCT04813354) with 2x2 complete block crossover design was conducted at three centers in the Netherlands and enrolled patients aged ≥18 years with mild-to-moderate asthma. Inclusion criteria

were inhaler use for ≥12 weeks prior to enrollment and naivety to ELLIPTA and BREEZHALER inhalers. Patients were randomized to ELLIPTA or BREEZHALER inhaler first and were assessed for errors in use of both inhalers after 1) reading PIL instructions, 2) receiving further instruction from a healthcare professional (HCP) if they made an error**.**
Results: 114 patients with asthma (57% female; mean age of 55.3 years) were assessed. After reading the PIL, 6% of patients made ≥1 critical error with ELLIPTA versus 26% with BREEZHALER (odds ratio [OR]: 0.11 [95% confidence interval (CI): 0.01-0.40]; p < 0.001). With ELLIPTA, 27% of patients made ≥1 overall error after reading the PIL versus 41% with BREEZHALER (OR: 0.25 [95% CI: 0.03-0.74]; p = 0.005). Fewer patients required HCP instruction with ELLIPTA than BREEZHALER (25% versus 32%).
Conclusions: Fewer patients made critical and overall errors using the ELLIPTA inhaler versus BREEZHALER after reading the PIL.

Gepubliceerd: Respir Med. 2022;205:107031.
Impact factor: 4.582 ; Q2

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32. Physical and mental fatigue in post-COVID syndrome and their associations over time: A small-sample ESM-study to explore fatigue, quality of sleep and behaviours
Wensink M, Schaap G, Ten Klooster PM, Doggen CJM, van der Palen J, Vonkeman HE, Bode C.

Objective: Post-COVID syndrome leaves millions of people with severe fatigue, yet little is known about its nature in daily life. In this exploratory study, momentary associations between physical and mental fatigue, quality of sleep and behaviours over two weeks in patients with post-COVID syndrome were assessed.
Method: Data on fatigue levels, quality of sleep and behaviours was collected for 14 consecutive days using the experience sampling method in ten ex-hospitalised patients with post-COVID syndrome**.**
Results: Multilevel linear regression modelling showed strong associations between physical and mental fatigue (β = 0.61, p ≤0.001), significant both between and within individuals. Sleeping more hours at night was associated with less physical and mental fatigue the following day (β = -0.35, p = .001; β = -0.27, p = .008). Strenuous relaxation (B = 0.45, p ≤0.001; B = 0.28, p = .004) and social contacts (B = -0.33, p = .003; B = -0.22, p = .02) were associated with physical and mental fatigue at the same measurement point. Performing household chores decreased physical and mental fatigue (B = -0.29, p = .02; B = -0.30, p = .006) two hours later on the same day, whereas eating and drinking increased physical fatigue (B = 0.20, p = .05) two hours later on the same day**.**
Conclusion: Physical fatigue and mental fatigue were strongly associated and revealed fluctuations in fatigue levels between individuals, which might suggest potentially different post-COVID subgroups. Indications for potential risk and beneficial behaviours for fatigue were found.

Gepubliceerd: J Psychosom Res. 2022;164:111084.
Impact factor: 4.620 ; Q2

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33. Assessing the Microcirculation of the Foot with Laser Speckle Contrast Imaging During Endovascular and Hybrid Revascularisation Procedures in Patients with Chronic Limb Threatening Ischaemia
Wermelink B, Mennes OA, Van Baal JG, Steenbergen W, Geelkerken RH, Study group includes: Aarnink SH; Beuk R; Brusse-Keiser M; Haalboom M; Meerwaldt R; Willigendael EM.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2022;63(6):898-9.

Impact factor: 6.427 ; Q1

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34. Paediatric COVID-19 mortality: a database analysis of the impact of health resource disparity
Marwali EM, Kekalih A, Yuliarto S, Wati DK, Rayhan M, Valerie IC, Cho HJ, Jassat W, Blumberg L, Masha M, Semple C, Swann OV, Kohns Vasconcelos M, Popielska J, Murthy S, Fowler RA, Guerguerian AM, Streinu-Cercel A, Pathmanathan MD, Rojek A, Kartsonaki C, Goncalves BP, Citarella BW, Merson L, Olliaro PL, Dalton HJ, International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Clinical Characterization Group Investigators; Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H

Background: The impact of the COVID-19 pandemic on paediatric populations varied between high-income countries (HICs) versus low-income to middle-income countries (LMICs). We sought to investigate differences in paediatric clinical outcomes and identify factors contributing to disparity between countries.
Methods: The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) COVID-19 database was queried to include children under 19 years of age admitted to hospital from January 2020 to April 2021 with suspected or confirmed COVID-19 diagnosis. Univariate and multivariable analysis of contributing factors for mortality were assessed by country group (HICs vs LMICs) as defined by the World Bank criteria.
Results: A total of 12 860 children (3819 from 21 HICs and 9041 from 15 LMICs) participated in this study. Of these, 8961 were laboratory-confirmed and 3899 suspected COVID-19 cases. About 52% of LMICs children were black, and more than 40% were infants and adolescent. Overall in-hospital mortality rate (95% CI) was 3.3% [=(3.0% to 3.6%), higher in LMICs than HICs (4.0% (3.6% to 4.4%) and 1.7% (1.3% to 2.1%), respectively). There were significant differences between country income groups in intervention profile, with higher use of antibiotics, antivirals, corticosteroids, prone positioning, high flow nasal cannula, non-invasive and invasive mechanical ventilation in HICs. Out of the 439 mechanically ventilated children, mortality occurred in 106 (24.1%) subjects, which was higher in LMICs than HICs (89 (43.6%) vs 17 (7.2%) respectively). Pre-existing infectious comorbidities (tuberculosis and HIV) and some complications (bacterial pneumonia, acute respiratory distress syndrome and myocarditis) were significantly higher in LMICs compared with HICs. On multivariable analysis, LMIC as country income group was associated with increased risk of mortality (adjusted HR 4.73 (3.16 to 7.10)).
Conclusion: Mortality and morbidities were higher in LMICs than HICs, and it may be attributable to differences in patient demographics, complications and access to supportive and treatment modalities.

Gepubliceerd: BMJ Paediatr Open. 2022;6(1).
Impact factor: 2.922; Q2

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35. Treating Rhythmic and Periodic EEG Patterns in Comatose Survivors of Cardiac Arrest
Ruijter BJ, Keijzer HM, Tjepkema-Cloostermans MC, Blans MJ, Beishuizen A, Tromp SC, Scholten E, Horn J, van Rootselaar AF, Admiraal MM, van den Bergh WM, Elting JJ, Foudraine NA, Kornips FHM, van Kranen-Mastenbroek V, Rouhl RPW, Thomeer EC, Moudrous W, Nijhuis FAP, Booij SJ, Hoedemaekers CWE, Doorduin J, Taccone FS, van der Palen J, van Putten M, Hofmeijer J, Telstar Investigators.

Background: Whether the treatment of rhythmic and periodic electroencephalographic (EEG) patterns in comatose survivors of cardiac arrest improves outcomes is uncertain.

Methods: We conducted an open-label trial of suppressing rhythmic and periodic EEG patterns detected on continuous EEG monitoring in comatose survivors of cardiac arrest. Patients were randomly assigned in a 1:1 ratio to a stepwise strategy of antiseizure medications to suppress this activity for at least 48 consecutive hours plus standard care (antiseizure-treatment group) or to standard care alone (control group); standard care included targeted temperature management in both groups. The primary outcome was neurologic outcome according to the score on the Cerebral Performance Category (CPC) scale at 3 months, dichotomized as a good outcome (CPC score indicating no, mild, or moderate disability) or a poor outcome (CPC score indicating severe disability, coma, or death). Secondary outcomes were mortality, length of stay in the intensive care unit (ICU), and duration of mechanical ventilation.
Results: We enrolled 172 patients, with 88 assigned to the antiseizure-treatment group and 84 to the control group. Rhythmic or periodic EEG activity was detected a median of 35 hours after cardiac arrest; 98 of 157 patients (62%) with available data had myoclonus. Complete suppression of rhythmic and periodic EEG activity for 48 consecutive hours occurred in 49 of 88 patients (56%) in the antiseizure-treatment group and in 2 of 83 patients (2%) in the control group. At 3 months, 79 of 88 patients (90%) in the antiseizure-treatment group and 77 of 84 patients (92%) in the control group had a poor outcome (difference, 2 percentage points; 95% confidence interval, -7 to 11; P = 0.68). Mortality at 3 months was 80% in the antiseizure-treatment group and 82% in the control group. The mean length of stay in the ICU and mean duration of mechanical ventilation were slightly longer in the antiseizure-treatment group than in the control group.
Conclusions: In comatose survivors of cardiac arrest, the incidence of a poor neurologic outcome at 3 months did not differ significantly between a strategy of suppressing rhythmic and periodic EEG activity with the use of antiseizure medication for at least 48 hours plus standard care and standard care alone.
(Funded by the Dutch Epilepsy Foundation; TELSTAR ClinicalTrials.gov number, NCT02056236.).

Gepubliceerd: N Engl J Med. 2022;386(8):724-34.
Impact factor: 176.082 ; Q1

Totale impact factor: 361.011
Gemiddelde impact factor: 10.315

Aantal artikelen 1e, 2e of laatste auteur: 6
Totale impact factor: 28.597
Gemiddelde impact factor: 4.766

Microbiologie

1. Who is providing HIV diagnostic testing? Comparing HIV testing by general practitioners and sexual health centres in five regions in the Netherlands, 2011-2018
Bogers SJ, Twisk DE, Beckers LM, Götz HM, Meima B, Kroone M, Hoornenborg E, Ott A, Luning-Koster MN, Dukers-Muijrers N, Hoebe C, Kampman CJG, Bosma F, Schim van der Loeff M, Geerlings S, van Bergen J.

Objectives: General practitioners (GPs) and sexual health centres (SHCs) are the main providers of HIV testing and diagnose two-thirds of HIV infections in the Netherlands. We compared regional HIV testing and positivity by GPs versus SHCs to gain insight into strategies to improve HIV testing, to enable timely detection of HIV infections**.**
Methods: Laboratory data (2011-2018) on HIV testing by GPs and SHCs in five Dutch regions with varying levels of urbanisation were evaluated. Regional HIV testing rates per 10 000 residents ≥15 years (mean over period and annual) were compared between providers using negative binomial generalised additive models and additionally stratified by sex and age (15-29 years, 30-44 years, 45-59 years, ≥60 years). $\chi(2)$ tests were used to compare positivity percentage between the two groups of providers**.**
Results: In the study period, 505 167 HIV tests (GP 36%, SHC 64%) were performed. The highest HIV testing rates were observed in highly urbanised regions, with large regional variations. The HIV testing rates ranged from 28 to 178 per 10 000 residents by GPs and from 30 to 378 per 10 000 by SHCs. Testing rates by GPs were lower than by SHCs in three regions and comparable in two. In all regions, men were tested less by GPs than by SHCs; for women, this varied by region. Among those aged 15-29 years old, GPs' testing rates were lower than SHCs', while this was reversed in older age categories in four out of five regions. The overall mean HIV positivity was 0.4%. In contrast to other regions, positivity in Amsterdam was significantly higher among individuals tested by GPs than by SHCs.
Conclusions: This retrospective observational study shows that besides SHCs, who perform opt-out testing for key groups, GPs play a prominent role in HIV testing, especially in non-key populations, such as women and older individuals. Large regional variation exists, requiring region-specific interventions to improve GPs' HIV testing practices.

Gepubliceerd: Sex Transm Infect. 2022;98(4):262-8.
Impact factor: 4.199 ; Q3

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2. Respiratory Syncytial Virus, Human Metapneumovirus, and Parainfluenza Virus Infections in Lung Transplant Recipients: A Systematic Review of Outcomes and Treatment Strategies
de Zwart A, Riezebos-Brilman A, Lunter G, Vonk J, Glanville AR, Gottlieb J, Permpalung N, Kerstjens H, Alffenaar JW, Verschuuren E.

Background: Respiratory syncytial virus (RSV), parainfluenza virus (PIV), and human metapneumovirus (hMPV) are increasingly associated with chronic lung allograft dysfunction (CLAD) in lung transplant recipients (LTR). This systematic review primarily aimed to assess outcomes of RSV/PIV/hMPV infections in LTR and secondarily to assess evidence regarding the efficacy of ribavirin**.**
Methods: Relevant databases were queried and study outcomes extracted using a standardized method and summarized**.**
Results: Nineteen retrospective and 12 prospective studies were included (total 1060 cases). Pooled 30-day mortality was low (0-3%), but CLAD progression 180-360 days postinfection was substantial (pooled incidences 19-24%) and probably associated with severe infection. Ribavirin trended toward

effectiveness for CLAD prevention in exploratory meta-analysis (odds ratio [OR] 0.61, [0.27-1.18]), although results were highly variable between studies.
Conclusions: RSV/PIV/hMPV infection was followed by a high CLAD incidence. Treatment options, including ribavirin, are limited. There is an urgent need for high-quality studies to provide better treatment options for these infections.

Gepubliceerd: Clin Infect Dis. 2022;74(12):2252-60.
Impact factor: 20.999; Q1

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3. Impact of COVID-19 social distancing measures on lung transplant recipients: decline in overall respiratory virus infections is associated with stabilisation of lung function
de Zwart AES, Riezebos-Brilman A, Lunter GA, Neerken ECU, van Leer-Buter CC, Alffenaar JC, van Gemert AP, Erasmus ME, Gan CT, Kerstjens HAM, Vonk JM, Verschuuren EAM.

Background: Coronavirus disease 2019 (COVID-19) social distancing measures led to a dramatic decline in non-COVID-19 respiratory virus infections, providing a unique opportunity to study their impact on annual forced expiratory volume in 1 s (FEV(1)) decline, episodes of temporary drop in lung function (TDLF) suggestive of infection and chronic lung allograft dysfunction (CLAD) in lung transplant recipients (LTRs)**.**
Methods: All FEV(1) values of LTRs transplanted between 2009 and April 2020 at the University Medical Center Groningen (Groningen, The Netherlands) were included. Annual FEV(1) change was estimated with separate estimates for pre-social distancing (2009-2020) and the year with social distancing measures (2020-2021). Patients were grouped by individual TDLF frequency (frequent/infrequent). Respiratory virus circulation was derived from weekly hospital-wide respiratory virus infection rates. Effect modification by TDLF frequency and respiratory virus circulation was assessed. CLAD and TDLF rates were analysed over time**.**
Results: 479 LTRs (12 775 FEV(1) values) were included. Pre-social distancing annual change in FEV(1) was -114 (95% CI -133- -94) mL, while during social distancing FEV(1) did not decline: 5 (95% CI -38-48) mL (difference pre-social distancing versus during social distancing: p<0.001). The frequent TDLF subgroup showed faster annual FEV(1) decline compared with the infrequent TDLF subgroup (-150 (95% CI -181- -120) versus -90 (95% CI -115- -65) mL; p=0.003). During social distancing, we found significantly lower odds for any TDLF (OR 0.53, 95% CI 0.33-0.85; p=0.008) and severe TDLF (OR 0.34, 0.16-0.71; p=0.005) as well as lower CLAD incidence (OR 0.53, 95% CI 0.27-1.02; p=0.060). Effect modification by respiratory virus circulation indicated a significant association between TDLF/CLAD and respiratory viruses.
Conclusions: During COVID-19 social distancing the strong reduction in respiratory virus circulation coincided with markedly less FEV(1) decline, fewer episodes of TDLF and possibly less CLAD. Effect modification by respiratory virus circulation suggests an important role for respiratory viruses in lung function decline in LTRs.

Gepubliceerd: Eur Respir J. 2022;60(5).
Impact factor: 33.801 ; Q1

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4. ISARIC-COVID-19 dataset: A Prospective, Standardized, Global Dataset of Patients Hospitalized with COVID-19
Garcia-Gallo E, Merson L, Kennon K, Kelly S, Citarella BW, Fryer DV, Shrapnel S, Lee J, Duque S, Fuentes YV, Balan V, Smith S, Wei J, Gonçalves BP, Russell CD, Sigfrid L, Dagens A, Olliaro PL, Baruch J, Kartsonaki C, Dunning J, Rojek A, Rashan A, Beane A, Murthy S, Reyes LF, ISARIC Clinical

Characterization Group: Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H.

The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) COVID-19 dataset is one of the largest international databases of prospectively collected clinical data on people hospitalized with COVID-19. This dataset was compiled during the COVID-19 pandemic by a network of hospitals that collect data using the ISARIC-World Health Organization Clinical Characterization Protocol and data tools. The database includes data from more than 705,000 patients, collected in more than 60 countries and 1,500 centres worldwide. Patient data are available from acute hospital admissions with COVID-19 and outpatient follow-ups. The data include signs and symptoms, pre-existing comorbidities, vital signs, chronic and acute treatments, complications, dates of hospitalization and discharge, mortality, viral strains, vaccination status, and other data. Here, we present the dataset characteristics, explain its architecture and how to gain access, and provide tools to facilitate its use.

Gepubliceerd: Sci Data. 2022;9(1):454.
Impact factor: 8.501 ; Q1

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5. Validation and verification of the GeneFinder™ COVID-19 Plus RealAmp kit on the ELITe InGenius® instrument
Gard L, Fliss MA, Bosma F, Ter Veen D, Niesters HGM.

Background: Throughout the SARS-CoV-2 pandemic, a rapid identification of the virus was essential to quickly recognize positive cases and limit further spread by applying appropriate infection prevention. Many diagnostic laboratories use a multiplex Real-Time PCR assay, as they are not only highly sensitive but also specific. Currently, there are several assays and platforms in the market available which target different SARS-CoV-2 genes. The aim of this study was to validate and verify the GeneFinder™ COVID-19 PLUS RealAmp kit on the ELITe InGenius® instrument and compare to the national reference method**.**
Methods: GeneFinder™ COVID-19 PLUS RealAmp kit was evaluated against the routine WHO in-house Real-Time PCR assay, which is also the national reference method in the Netherlands and used in our laboratory. The sensitivity was tested using the analytical panel from Qnostics (Glasgow, United Kingdom) and the specificity was tested with patient material comprising of other seasonal respiratory viruses. In addition, 96 clinical samples initially analyzed by routine Real-Time PCR were tested using the GeneFinder™ COVID-19 PLUS RealAmp kit on the ELITe InGenius® instrument**.**
Results: The GeneFinder™ COVID-19 PLUS RealAmp kit had a similar performance compared to routine in-house testing, with a limit of detection of 500 dC/mL for the RdRp-gene and E gene. Meanwhile, the N gene showed a limit of detection of 50 dC/mL. The SARS-CoV-2 test was highly specific and detected no other respiratory viruses. The results of the clinical samples were comparable between both assays with similar Ct values observed for the in-house Real-Time-PCR and the GeneFinder™ COVID-19 PLUS RealAmp kit for the N gene**.**
Conclusion: The GeneFinder™ COVID-19 PLUS RealAmp kit on the ELITe InGenius® instrument had an appropriate sensitivity and specificity that could be used in small scale laboratories or during night shifts where accurate diagnostics are crucial.

Gepubliceerd: J Virol Methods. 2022;300:114378.
Impact factor: 2.623 ; Q3

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6. Defining a risk area for tick-borne encephalitis (TBE) in a country where TBE is emerging, the Netherlands, July 2016-October 2020
Geeraedts F, Wertenbroek A, de Klerk J, Prick JJ, Reichman LJA, Hess D, Bosma F, Reimerink J, Skidmore B, Laverman GD.

TBE is an emerging infectious disease in the Netherlands since July 2016, and risk areas have not been defined yet. Until October 2020 twelve autochthonous cases of TBE have been identified. In six of these cases transmission of TBE virus likely occurred in the Twente region, which therefore is the region with the highest case number and risk of contracting the disease. Here we summarize the Twente cases so far and discuss if the Twente region should be considered a risk-area using criteria of traditional TBE endemic countries, and the public health measures that may accompany such designation.

Gepubliceerd: Ticks Tick Borne Dis. 2022;13(2):101898.
Impact factor: 3.817 ; Q1

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7. A prospective multicentre screening study on multidrug-resistant organisms in intensive care units in the Dutch-German cross-border region, 2017 to 2018: the importance of healthcare structures
Glasner C, Berends MS, Becker K, Esser J, Gieffers J, Jurke A, Kampinga G, Kampmeier S, Klont R, Köck R, von Müller L, Al Naemi N, Ott A, Ruijs G, Saris K, Tami A, Voss A, Waar K, van Zeijl J, Friedrich AW.

Background: Antimicrobial resistance poses a risk for healthcare, both in the community and hospitals. The spread of multidrug-resistant organisms (MDROs) occurs mostly on a local and regional level, following movement of patients, but also occurs across national borders.AimThe aim of this observational study was to determine the prevalence of MDROs in a European cross-border region to understand differences and improve infection prevention based on real-time routine data and workflows.
Methods: Between September 2017 and June 2018, 23 hospitals in the Dutch (NL)-German (DE) cross-border region (BR) participated in the study. During 8 consecutive weeks, patients were screened upon admission to intensive care units (ICUs) for nasal carriage of meticillin-resistant Staphylococcus aureus (MRSA) and rectal carriage of vancomycin-resistant Enterococcus faecium/E. faecalis (VRE), third-generation cephalosporin-resistant Enterobacteriaceae (3GCRE) and carbapenem-resistant Enterobacteriaceae (CRE). All samples were processed in the associated laboratories.
Results: A total of 3,365 patients were screened (median age: 68 years (IQR: 57-77); male/female ratio: 59.7/40.3; NL-BR: n = 1,202; DE-BR: n = 2,163). Median screening compliance was 60.4% (NL-BR: 56.9%; DE-BR: 62.9%). MDRO prevalence was higher in DE-BR than in NL-BR, namely 1.7% vs 0.6% for MRSA ($p = 0.006$), 2.7% vs 0.1% for VRE ($p < 0.001$) and 6.6% vs 3.6% for 3GCRE ($p < 0.001$), whereas CRE prevalence was comparable (0.2% in DE-BR vs 0.0% in NL-BR ICUs).
Conclusions: This first prospective multicentre screening study in a European cross-border region shows high heterogenicity in MDRO carriage prevalence in NL-BR and DE-BR ICUs. This indicates that the prevalence is probably influenced by the different healthcare structures.

Gepubliceerd: Euro Surveill. 2022;27(5).
Impact factor: 21.286 ; Q1

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8. Hepatitis C Elimination in the Netherlands (CELINE): How nationwide retrieval of lost to follow-up hepatitis C patients contributes to micro-elimination

Isfordink CJ, van Dijk M, Brakenhoff SM, Kracht PAM, Arends JE, de Knegt RJ, van der Valk M, Drenth JPH, CELINE Study Group; Venneman N.G, Bosma F.

Background & Aims: The number of chronic hepatitis C virus (HCV)-infected patients who have been lost to follow-up (LTFU) is high and threatens HCV elimination. Micro-elimination focusing on the LTFU population is a promising strategy for low-endemic countries like the Netherlands (HCV prevalence 0.16%). We therefore initiated a nationwide retrieval project in the Netherlands targeting LTFU HCV patients**.**
Methods: LTFU HCV-infected patients were identified using laboratory and patient records. Subsequently, the Municipal Personal Records database was queried to identify individuals eligible for retrieval, defined as being alive and with a known address in the Netherlands. These individuals were invited for re-evaluation. The primary endpoint was the number of patients successfully re-linked to care**.**
Results: Retrieval was implemented in 45 sites in the Netherlands. Of 20,183 ever-diagnosed patients, 13,198 (65%) were known to be cured or still in care and 1,537 (8%) were LTFU and eligible for retrieval. Contact was established with 888/1,537 (58%) invited individuals; 369 (24%) had received prior successful treatment elsewhere, 131 (9%) refused re-evaluation and 251 (16%) were referred for re-evaluation. Finally, 219 (14%) were re-evaluated, of whom 172 (79%) approved additional data collection. HCV-RNA was positive in 143/172 (83%), of whom 38/143 (27%) had advanced fibrosis or cirrhosis and 123/143 (86%) commenced antiviral treatment**.**
Conclusion: Our nationwide micro-elimination strategy accurately mapped the ever-diagnosed HCV population in the Netherlands and indicates that 27% of LTFU HCV-infected patients re-linked to care have advanced fibrosis or cirrhosis. This emphasizes the potential value of systematic retrieval for HCV elimination.

Gepubliceerd: Eur J Intern Med. 2022;101:93-7.
Impact factor: 7.749 ; Q1

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9. Respiratory support in patients with severe COVID-19 in the International Severe Acute Respiratory and Emerging Infection (ISARIC) COVID-19 study: a prospective, multinational, observational study

Reyes LF, Murthy S, Garcia-Gallo E, Merson L, Ibáñez-Prada ED, Rello J, Fuentes YV, Martin-Loeches I, Bozza F, Duque S, Taccone FS, Fowler RA, Kartsonaki C, Gonçalves BP, Citarella BW, Aryal D, Burhan E, Cummings MJ, Delmas C, Diaz R, Figueiredo-Mello C, Hashmi M, Panda PK, Jiménez MP, Rincon DFB, Thomson D, Nichol A, Marshall JC, Olliaro PL, ISARIC Characterization Group: Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H..

Background: Up to 30% of hospitalised patients with COVID-19 require advanced respiratory support, including high-flow nasal cannulas (HFNC), non-invasive mechanical ventilation (NIV), or invasive mechanical ventilation (IMV). We aimed to describe the clinical characteristics, outcomes and risk factors for failing non-invasive respiratory support in patients treated with severe COVID-19 during the first two years of the pandemic in high-income countries (HICs) and low middle-income countries (LMICs)**.**
Methods: This is a multinational, multicentre, prospective cohort study embedded in the ISARIC-WHO COVID-19 Clinical Characterisation Protocol. Patients with laboratory-confirmed SARS-CoV-2 infection who required hospital admission were recruited prospectively. Patients treated with HFNC, NIV, or IMV within the first 24 h of hospital admission were included in this study. Descriptive statistics, random forest, and logistic regression analyses were used to describe clinical characteristics and compare clinical outcomes among patients treated with the different types of advanced respiratory support**.**

Results: A total of 66,565 patients were included in this study. Overall, 82.6% of patients were treated in HIC, and 40.6% were admitted to the hospital during the first pandemic wave. During the first 24 h after hospital admission, patients in HICs were more frequently treated with HFNC (48.0%), followed by NIV (38.6%) and IMV (13.4%). In contrast, patients admitted in lower- and middle-income countries (LMICs) were less frequently treated with HFNC (16.1%) and the majority received IMV (59.1%). The failure rate of non-invasive respiratory support (i.e. HFNC or NIV) was 15.5%, of which 71.2% were from HIC and 28.8% from LMIC. The variables most strongly associated with non-invasive ventilation failure, defined as progression to IMV, were high leukocyte counts at hospital admission (OR [95%CI]; 5.86 [4.83-7.10]), treatment in an LMIC (OR [95%CI]; 2.04 [1.97-2.11]), and tachypnoea at hospital admission (OR [95%CI]; 1.16 [1.14-1.18]). Patients who failed HFNC/NIV had a higher 28-day fatality ratio (OR [95%CI]; 1.27 [1.25-1.30]).
Conclusions: In the present international cohort, the most frequently used advanced respiratory support was the HFNC. However, IMV was used more often in LMIC. Higher leucocyte count, tachypnoea, and treatment in LMIC were risk factors for HFNC/NIV failure. HFNC/NIV failure was related to worse clinical outcomes, such as 28-day mortality. Trial registration This is a prospective observational study; therefore, no health care interventions were applied to participants, and trial registration is not applicable.

Gepubliceerd: Crit Care. 2022;26(1):276.
Impact factor: 19.344; Q1

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10. Longitudinal monitoring of BKPyV miRNA levels in kidney transplant recipients with BKPyV-related pathology reflects viral DNA levels and remain high in viremia patients after clearance of viral DNA
van Doesum WB, Gard L, Knijff LWD, Niesters HGM, van Son WJ, Stegeman CA, van den Berg A, Groen H, van den Born J, Riezebos-Brilman A, Sanders JS.

Introduction: It is unclear whether polyomavirus BK (BKPyV) microribonucleic acid (miRNA) measurement has additional diagnostic and predictive value in kidney transplant recipients (KTR) as compared to current methods of monitoring BKPyV DNA loads.
Patients and Methods: A retrospective, longitudinal study was performed in 30 KTR with BKPyV viruria (n = 10), BKPyV viremia (n = 10), or BKPyV-associated neuropathy (BKPyVAN) (n = 10). Bkv-miR-B1-3p and 5p and BKPyV DNA load were measured in urine and plasma and compared using receiver operating characteristic (ROC) curves**.**
Results: Levels of Bkv-miR-B1-3p and 5p and BKPyV DNA correlated strongly. Overall, mostly analog courses of urinary and plasma miRNA and DNA loads were observed. Areas under the ROC curves were not significantly different between miRNAs and DNA. Only, in contrast to BKPyV DNA load, BKPyV miRNA levels increased from 6 to 12 months in the viremia group, while in the BKPyVAN group, a decline was seen in both DNA and miRNA.
Conclusions: In this study, we could not demonstrate an additional value of BKPyV miRNA detection compared to BKPyV DNA monitoring in the early phase after kidney transplantation. We did observe significant differences between the viremia and the BKPyVAN groups during follow-up. This study was performed with a small number of patients and therefore results should be verified in a larger patient cohort. Furthermore, future studies with larger patient groups are necessary to elucidate final clinical value of these data.

Gepubliceerd: Transpl Infect Dis. 2022;24(6):e13927.
Impact factor: 2.867 ; Q3

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11. The association between viral load and concurrent human papillomavirus infection at the genital and anal sites of young women and the impact of vaccination
van Eer K, Laâbi I, van Benthem BHB, Steenbergen RDM, King AJ, Medical Microbiological Laboratories, LabMicTa; Bosma F.

Concurrent genital-anal human papillomavirus (HPV) infections may impose an increased anal cancer risk in women with HPV-related genital lesions. High viral load may facilitate genital-anal HPV concurrence. Genital and anal HPV is reduced by a bivalent HPV16/18 vaccine, yet the effect on concurrent genital-anal HPV remains unclear. This study analyzed viral load in concurrent genital-anal HPV infections, relative to genital-only and anal-only HPV infections and the impact of vaccination in young women. We included 1074 women, who provided both genital and anal swabs. HPV detection and genotyping was performed using the SPF10-DEIA-LiPA25. HPV copy numbers were measured with type-specific qPCRs and corrected for cellular content to obtain the viral load. Concurrent genital-anal HPV often had significantly higher genital viral load (0.09-371 c/cell) than genital-only HPV (3.17E-04-15.9 c/cell, $p < 0.0001$ to $p < 0.05$). Moreover, nearly all concurrent genital-anal HPV types had higher genital copy numbers per PCR reaction (157-416E04 c/rxn) than anal copy numbers (0.90-884E01 c/rxn, $p < 0.0001$ to $p < 0.001$). Vaccinated women had significantly less infections with HPV16/18 vaccine-types (2.8% vs 13.7%, $p < 0.0001$) and HPV31/35/45 cross-protective types (7.4% vs 21.1%, $p < 0.0001$) than unvaccinated women. In conclusion, particularly high genital viral load is found in concurrent genital-anal HPV infections, which are effectively reduced by vaccination.

Gepubliceerd: Tumour Virus Res. 2022;13:200233.
Impact factor: 0 ; Q NVT

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19. Paediatric COVID-19 mortality: a database analysis of the impact of health resource disparity
Marwali EM, Kekalih A, Yuliarto S, Wati DK, Rayhan M, Valerie IC, Cho HJ, Jassat W, Blumberg L, Masha M, Semple C, Swann OV, Kohns Vasconcelos M, Popielska J, Murthy S, Fowler RA, Guerguerian AM, Streinu-Cercel A, Pathmanathan MD, Rojek A, Kartsonaki C, Goncalves BP, Citarella BW, Merson L, Olliaro PL, Dalton HJ, International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Clinical Characterization Group Investigators; Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H

Background: The impact of the COVID-19 pandemic on paediatric populations varied between high-income countries (HICs) versus low-income to middle-income countries (LMICs). We sought to investigate differences in paediatric clinical outcomes and identify factors contributing to disparity between countries.
Methods: The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) COVID-19 database was queried to include children under 19 years of age admitted to hospital from January 2020 to April 2021 with suspected or confirmed COVID-19 diagnosis. Univariate and multivariable analysis of contributing factors for mortality were assessed by country group (HICs vs LMICs) as defined by the World Bank criteria.
Results: A total of 12 860 children (3819 from 21 HICs and 9041 from 15 LMICs) participated in this study. Of these, 8961 were laboratory-confirmed and 3899 suspected COVID-19 cases. About 52% of LMICs children were black, and more than 40% were infants and adolescent. Overall in-hospital mortality rate (95% CI) was 3.3% [=(3.0% to 3.6%), higher in LMICs than HICs (4.0% (3.6% to 4.4%) and 1.7% (1.3% to 2.1%), respectively). There were significant differences between country income groups in intervention profile, with higher use of antibiotics, antivirals, corticosteroids, prone positioning, high flow nasal cannula, non-invasive and invasive mechanical ventilation in HICs. Out of the 439 mechanically ventilated children, mortality occurred in 106 (24.1%) subjects, which was higher in LMICs than HICs (89 (43.6%) vs 17 (7.2%) respectively). Pre-existing infectious comorbidities

(tuberculosis and HIV) and some complications (bacterial pneumonia, acute respiratory distress syndrome and myocarditis) were significantly higher in LMICs compared with HICs. On multivariable analysis, LMIC as country income group was associated with increased risk of mortality (adjusted HR 4.73 (3.16 to 7.10)).
Conclusion: Mortality and morbidities were higher in LMICs than HICs, and it may be attributable to differences in patient demographics, complications and access to supportive and treatment modalities.

Gepubliceerd: BMJ Paediatr Open. 2022;6(1).
Impact factor: 2.922; Q2

Totale impact factor: 128.108
Gemiddelde impact factor: 10.676

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 33.801
Gemiddelde impact factor: 33.801

Neurocentrum

1. Impact of the lockdown on acute stroke treatments during the first surge of the COVID-19 outbreak in the Netherlands
Benali F, Stolze LJ, Rozeman AD, Dinkelaar W, Coutinho JM, Emmer BJ, Gons RAR, Yo LFS, van Tuijl JH, Boukrab I, van Dam-Nolen DHK, van den Wijngaard IR, Lycklama À Nijeholt GJ, de Laat KF, van Dijk LC, den Hertog HM, Flach HZ, Wermer MJH, van Walderveen MAA, Brouwers P, Bulut T, Vermeer SE, Bernsen MLE, Uyttenboogaart M, Bokkers RPH, Boogaarts JD, de Leeuw FE, van der Worp HB, van der Schaaf IC, Schonewille WJ, Vos JA, Remmers MJM, Imani F, Dippel DWJ, van Zwam WH, Nederkoorn PJ, van Oostenbrugge RJ.

Introduction: We investigated the impact of the Corona Virus Disease 2019 (COVID-19) pandemic and the resulting lockdown on reperfusion treatments and door-to-treatment times during the first surge in Dutch comprehensive stroke centers. Furthermore, we studied the association between COVID-19-status and treatment times**.**
Methods: We included all patients receiving reperfusion treatment in 17 Dutch stroke centers from May 11th, 2017, until May 11th, 2020. We collected baseline characteristics, National Institutes of Health Stroke Scale (NIHSS) at admission, onset-to-door time (ODT), door-to-needle time (DNT), door-to-groin time (DGT) and COVID-19-status at admission. Parameters during the lockdown (March 15th, 2020 until May 11th, 2020) were compared with those in the same period in 2019, and between groups stratified by COVID-19-status. We used nationwide data and extrapolated our findings to the increasing trend of EVT numbers since May 2017**.**
Results: A decline of 14% was seen in reperfusion treatments during lockdown, with a decline in both IVT and EVT delivery. DGT increased by 12 min (50 to 62 min, p-value of < 0.001). Furthermore, median NIHSS-scores were higher in COVID-19 - suspected or positive patients (7 to 11, p-value of 0.004), door-to-treatment times did not differ significantly when stratified for COVID-19-status.
Conclusions: During the first surge of the COVID-19 pandemic, a decline in acute reperfusion treatments and a delay in DGT was seen, which indicates a target for attention. It also appeared that COVID-19-positive or -suspected patients had more severe neurologic symptoms, whereas their EVT-workflow was not affected.

Gepubliceerd: BMC Neurol. 2022;22(1):22.
Impact factor: 2.903 ; Q3

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2. Transient neurological deficit in patients with chronic subdural hematoma: a retrospective cohort analysis
Blaauw J, den Hertog HM, van Zundert JM, van der Gaag NA, Jellema K, Dammers R, Kho KH, Groen RJM, Lingsma HF, van der Naalt J, Jacobs B.

Rationale: Symptoms of chronic subdural hematoma (CSDH) vary widely, including transient neurological deficit(s) (TND). The precise prevalence and the clinical aspects of TND are yet to be determined. Most TNDs are regarded and treated as symptomatic seizures, but the rationale for this decision is not always clear**.**
Methods: Patients with temporary symptoms were selected from a retrospective cohort of CSDH patients. We analyzed the association of TND characteristics with patients being classified as having a symptomatic seizure and with functional outcome using logistic regression analysis**.**
Results: Of the included 1307 CSDH patients, 113 (8.6%) had at least one episode of TND. Most common TNDs were aphasia/dysphasia, impaired awareness or clonic movements. Of these 113 patients, 50 (44%) were diagnosed with symptomatic seizure(s) by their treating physician. Impaired awareness, clonic movements and the presence of 'positive symptoms' showed the strongest

association with the diagnosis symptomatic seizure (OR 36, 95% CI 7.8-163; OR 24, 95% CI 6.4-85; and OR 3.1, 95% CI 1.3-7.2). Aphasia/dysphasia lowered the chance of TND being classified as symptomatic seizure together with a longer TND duration (OR 0.2, 95% CI 0.1-0.6; and OR 0.91, 95% CI 0.84-0.99). Treatment with anti-epileptic drugs was related to unfavorable functional outcome (aOR 5.4, 95% CI 1.4-20.7)**.**
Conclusion: TND was not a rare phenomenon in our cohort of CSDH patients. A TND episode of 5 min, aphasia/dysphasia and/or absence of 'positive' symptoms are suggestive of a different TND pathophysiology than symptomatic seizures. Our results further suggest that treatment of TND in CSDH deserves careful consideration as management choices might influence patient outcome.

Gepubliceerd: J Neurol. 2022;269(6):3180-8.
Impact factor: 6.682 ; Q1

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3. Mortality after chronic subdural hematoma is associated with frailty
Blaauw J, Jacobs B, Hertog HMD, van der Gaag NA, Jellema K, Dammers R, Kho KH, Groen RJM, van der Naalt J, Lingsma HF.

Purpose: Chronic subdural hematoma (CSDH) is a common neurological disease often affecting the elderly. Long-term excess mortality for patients after CSDH has been suggested but causes of death are unknown. We hypothesize that excess mortality of CSDH patients is related to frailty. In this article, we describe mortality rates and causes of death of CSDH patients compared with the general population and assess the association of frailty with mortality**.**
Methods: A cohort study in which consecutive CSDH patients were compared to the general population regarding mortality rates. Furthermore, the association of six frailty indicators (cognitive problems, frequent falling, unable to live independently, unable to perform daily self-care, use of benzodiazepines or psychotropic drugs, and number of medications) with mortality was assessed**.**
Results: A total of 1307 CSDH patients were included, with a mean age of 73.7 (SD ± 11.4) years and 958 (73%) were male. Median follow-up was 56 months (range: 0-213). Compared with controls CSDH patients had a hazard ratio for mortality of 1.34 (95% CI: 1.2-1.5). CSDH patients more often died from cardiovascular diseases (37% vs. 30%) and falls (7.2% vs. 3.7%). Among CSDH patients frequent falling (HR 1.3; 95% CI: 1.0-1.7), inability to live independently (HR 1.4, 95% CI: 1.1-1.8), inability to perform daily self-care (HR 1.5; 95% CI: 1.1-1.9), and number of medications used (HR 1.0; 95% CI: 1.0-1.1) were independently associated with mortality.
Conclusions: CSDH patients have higher mortality rates than the general population. Frailty in CSDH patients is associated with higher mortality risk. More attention for the frailty of CSDH patients is warranted.

Gepubliceerd: Acta Neurochir (Wien). 2022;164(12):3133-41.
Impact factor: 2.816 ; Q2

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4. Presenting symptoms and functional outcome of chronic subdural hematoma patients
Blaauw J, Meelis GA, Jacobs B, van der Gaag NA, Jellema K, Kho KH, Groen RJM, van der Naalt J, Lingsma HF, den Hertog HM.

Background: Patients with chronic subdural hematoma (CSDH) can present with a variety of signs and symptoms. The relationship of these signs and symptoms with functional outcome is unknown. Knowledge of these associations might aid clinicians in the choice to initiate treatment and may allow them to better inform patients on expected outcomes.

Objective: To investigate if presenting signs and symptoms influence functional outcome in patients with CSDH**.**
Methods: We conducted a retrospective analysis of consecutive CSDH patients in three hospitals. Glasgow Outcome Scale Extended (GOS-E) scores were obtained from the first follow-up visit after treatment. An ordinal multivariable regression analysis was performed, to assess the relationship between the different signs and symptoms on the one hand and functional outcome on the other adjusted for potential confounders**.**
Results: We included 1,307 patients, of whom 958 (73%) were male and mean age was 74 (SD ± 11) years. Cognitive complaints were associated with lower GOS-E scores at follow-up (aOR 0.7, 95% CI: 0.5 - 0.8) Headache and higher Glasgow Coma Scale (GCS) scores were associated with higher GOS-E scores. (aOR 1.9, 95% CI: 1.5-2.3 and aOR 1.3, 95% CI: 1.2-1.4)**.**
Conclusion: Cognitive complaints are independently associated with worse functional outcome, whereas headache and higher GCS scores are associated with better outcome. The increased probability of unfavorable outcome in patients with CSDH who present with cognitive complaints favors a more prominent place of assessing cognitive status at diagnosis.

Gepubliceerd: Acta Neurol Scand. 2022;145(1):38-46.
Impact factor: 3.915 ; Q2

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5. Neuroimaging Parameters Are Not Associated With Chronic Post-stroke Fatigue in Young Stroke Patients
Boot EM, van de Camp S, Maaijwee NA, Arntz RM, Kessels RPC, de Leeuw FE, Tuladhar AM.

Introduction: Post-stroke fatigue is frequently present in young adults, but its underlying mechanism is still unclear. The aim of the study was to investigate the association between lesion location, network efficiency and chronic post-stroke fatigue based on voxel-based lesion-symptom mapping and structural network connectivity analysis.
Patients and Methods: One hundred and thirty five young patients, aged 18-50 years, with a first-ever transient ischemic attack or cerebral infarction from the Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation (FUTURE) study, underwent 1.5T MRI and were assessed for fatigue using the self-report Checklist Individual Strength. Stroke lesions were manually segmented, and structural network efficiency was calculated using the diffusion MRI-based brain networks and graph theory for each patient. Univariate and multivariate analyses was performed to study the associations between MRI parameters and chronic post-stroke fatigue. In addition, we used voxel-based lesion-symptom mapping to analyze the relationship between the lesion location and chronic post-stroke fatigue**.**
Results: Mean age at index event was 39.0 years (SD ± 8.2), and mean follow-up duration was 11.0 years (SD ± 8.0). 50 patients (37%) had post-stroke fatigue. Voxel-based lesion-symptom mapping showed no significant relation between stroke lesions and the presence of chronic post-stroke fatigue. Furthermore, there were no significant associations between the lesion size or network efficiency, and the presence of chronic post-stroke fatigue.
Discussion: We did not find any association between stroke characteristics (lesion location and size) and chronic post-stroke fatigue (CIS20-R), nor associations between structural brain network connectivity and post-stroke fatigue on the long term in young stroke patients.

Gepubliceerd: Front Neurol. 2022;13:831357.
Impact factor: 4.086 ; Q2

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6. The Gray Area of Freezing of Gait Annotation: A Guideline and Open-Source Practical Tool

Cockx H, Klaver E, Tjepkema-Cloostermans M, van Wezel R, Nonnekes J.

Background: Freezing of gait, a disabling episodic symptom, is difficult to assess as the exact begin- and endpoint of an episode is not easy to specify. This hampers scientific and clinical progress. The current golden standard is video annotation by two independent raters. However, the comparison of the two ratings gives rise to non-overlapping, gray areas.
Objective: To provide a guideline for dealing with these gray areas.
Methods/results: We propose a standardized procedure for handling the gray areas based on two parameters, the tolerance and correction parameter. Furthermore, we recommend the use of positive agreement, negative agreement, and prevalence index to report interrater agreement instead of the commonly used intraclass correlation coefficient or Cohen's kappa. This theoretical guideline was implemented in an open-source practical tool, FOGtool (https://github.com/helenacockx/FOGtool)**.**
Conclusion: This paper aims to contribute to the standardization of freezing of gait assessment, thereby improving data sharing procedures and replicability of study results.

Gepubliceerd: Mov Disord Clin Pract. 2022;9(8):1099-104.
Impact factor: 4.514 ; Q2

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7. Improvements in Endovascular Treatment for Acute Ischemic Stroke: A Longitudinal Study in the MR CLEAN Registry

Compagne KCJ, Kappelhof M, Hinsenveld WH, Brouwer J, Goldhoorn RB, Uyttenboogaart M, Bokkers RPH, Schonewille WJ, Martens JM, Hofmeijer J, van der Worp HB, Lo RTH, Keizer K, Yo LSF, Lycklama À Nijeholt GJ, den Hertog HM, Sturm EJC, Brouwers P, van Walderveen MAA, Wermer MJH, de Bruijn SF, van Dijk LC, Boogaarts HD, van Dijk EJ, van Tuijl JH, Peluso JPP, de Kort PLM, van Hasselt B, Fransen PS, Schreuder T, Heijboer RJJ, Jenniskens SFM, Sprengers MES, Ghariq E, van den Wijngaard IR, Roosendaal SD, Meijer A, Beenen LFM, Postma AA, van den Berg R, Yoo AJ, van Doormaal PJ, van Proosdij MP, Krietemeijer MGM, Gerrits DG, Hammer S, Vos JA, Boiten J, Coutinho JM, Emmer BJ, van Es A, Roozenbeek B, Roos Y, van Zwam WH, van Oostenbrugge RJ, Majoie C, Dippel DWJ, van der Lugt A.

Background: We evaluated data from all patients in the Netherlands who underwent endovascular treatment for acute ischemic stroke in the past 3.5 years, to identify nationwide trends in time to treatment and procedural success, and assess their effect on clinical outcomes**.**
Methods: We included patients with proximal occlusions of the anterior circulation from the second and first cohorts of the MR CLEAN (Multicenter Randomized Clinical trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry (March 2014 to June 2016; June 2016 to November 2017, respectively). We compared workflow times and rates of successful reperfusion (defined as an extended Thrombolysis in Cerebral Infarction score of 2B-3) between cohorts and chronological quartiles (all included patients stratified in chronological quartiles of intervention dates to create equally sized groups over the study period). Multivariable ordinal logistic regression was used to assess differences in the primary outcome (ordinal modified Rankin Scale at 90 days)**.**
Results: Baseline characteristics were similar between cohorts (second cohort n=1692, first cohort n=1488) except for higher age, poorer collaterals, and less signs of early ischemia on computed tomography in the second cohort. Time from stroke onset to groin puncture and reperfusion were shorter in the second cohort (median 185 versus 210 minutes; P<0.001 and 236 versus 270 minutes; P<0.001, respectively). Successful reperfusion was achieved more often in the second than in the first cohort (72% versus 66%; P<0.001). Functional outcome significantly improved (adjusted common odds ratio 1.23 [95% CI, 1.07-1.40]). This effect was attenuated by adjustment for time from onset to reperfusion (adjusted common odds ratio, 1.12 [95% CI, 0.98-1.28]) and successful

reperfusion (adjusted common odds ratio, 1.13 [95% CI, 0.99-1.30]). Outcomes were consistent in the analysis per chronological quartile.
Conclusions: Clinical outcomes after endovascular treatment for acute ischemic stroke in routine clinical practice have improved over the past years, likely resulting from improved workflow times and higher successful reperfusion rates.

Gepubliceerd: Stroke. 2022;53(6):1863-72.
Impact factor: 10.170 ; Q1

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8. Commentary: Autoimmune diseases in patients with myotonic dystrophy type 2
Damen MJ, den Broeder AA, Voermans NC, Tieleman AA.

Gepubliceerd: Front Neurol. 2022;13:1041437.
Impact factor: 4.086 ; Q2

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9. Hospital Variation in Time to Endovascular Treatment for Ischemic Stroke: What Is the Optimal Target for Improvement?
den Hartog SJ, Lingsma HF, van Doormaal PJ, Hofmeijer J, Yo LSF, Majoie C, Dippel DWJ, van der Lugt A, Roozenbeek B, MR CLEAN Registry investigators; Brouwers PJAM.

Background: Time to reperfusion in patients with ischemic stroke is strongly associated with functional outcome and may differ between hospitals and between patients within hospitals. Improvement in time to reperfusion can be guided by between-hospital and within-hospital comparisons and requires insight in specific targets for improvement. We aimed to quantify the variation in door-to-reperfusion time between and within Dutch intervention hospitals and to assess the contribution of different time intervals to this variation**.**
Methods and Results: We used data from the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry. The door-to-reperfusion time was subdivided into time intervals, separately for direct patients (door-to-computed tomography, computed tomography-to-computed tomography angiography [CTA], CTA-to-groin, and groin-to-reperfusion times) and for transferred patients (door-to-groin and groin-to-reperfusion times). We used linear mixed models to distinguish the variation in door-to-reperfusion time between hospitals and between patients. The proportional change in variance was used to estimate the amount of variance explained by each time interval. We included 2855 patients of 17 hospitals providing endovascular treatment. Of these patients, 44% arrived directly at an endovascular treatment hospital. The between-hospital variation in door-to-reperfusion time was 9%, and the within-hospital variation was 91%. The contribution of case-mix variables on the variation in door-to-reperfusion time was marginal (2%-7%). Of the between-hospital variation, CTA-to-groin time explained 83%, whereas groin-to-reperfusion time explained 15%. Within-hospital variation was mostly explained by CTA-to-groin time (33%) and groin-to-reperfusion time (42%). Similar results were found for transferred patients**.**
Conclusions: Door-to-reperfusion time varies between, but even more within, hospitals providing endovascular treatment for ischemic stroke. Quality of stroke care improvements should not only be guided by between-hospital comparisons, but also aim to reduce variation between patients within a hospital, and should specifically focus on CTA-to-groin time and groin-to-reperfusion time.

Gepubliceerd: J Am Heart Assoc. 2022;11(1):e022192.
Impact factor: 6.107 ; Q2

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10. Effectiveness and implementation of SHared decision-making supported by OUTcome information among patients with breast cancer, stroke and advanced kidney disease: SHOUT study protocol of multiple interrupted time series
Hackert MQN, Ankersmid JW, Engels N, Prick JCM, Teerenstra S, Siesling S, Drossaert CHC, Strobbe LJA, van Riet YEA, van den Dorpel RMA, Bos WJW, van der Nat PB, van den Berg-Vos RM, van Schaik SM, Garvelink MM, van der Wees PJ, van Uden-Kraan CF, Santeon VBHC breast cancer, stroke and chronic kidney disease group; Brinkman JN, Brouwers PJAM, Dassen AE.

Introduction: Within the value-based healthcare framework, outcome data can be used to inform patients about (treatment) options, and empower them to make shared decisions with their health care professional. To facilitate shared decision-making (SDM) supported by outcome data, a multicomponent intervention has been designed, including patient decision aids on the organisation of post-treatment surveillance (breast cancer); discharge location (stroke) and treatment modality (advanced kidney disease), and training on SDM for health care professionals. The SHared decision-making supported by OUTcome information (SHOUT) study will examine the effectiveness of the intervention and its implementation in clinical practice.
Methods and Analysis: Multiple interrupted time series will be used to stepwise implement the intervention. Patients diagnosed with either breast cancer (N=630), stroke (N=630) or advanced kidney disease (N=473) will be included. Measurements will be performed at baseline, three (stroke), six and twelve (breast cancer and advanced kidney disease) months. Trends on outcomes will be measured over a period of 20 months. The primary outcome will be patients' perceived level of involvement in decision-making. Secondary outcomes regarding effectiveness will include patient-reported SDM, decisional conflict, role in decision-making, knowledge, quality of life, preferred and chosen care, satisfaction with the intervention, healthcare utilisation and health outcomes. Outcomes regarding implementation will include the implementation rate and a questionnaire on the health care professionals' perspective on the implementation process.
Ethics and Dissemination: The Medical research Ethics Committees United in Nieuwegein, the Netherlands, has confirmed that the Medical Research Involving Human Subjects Act does not apply to this study. Bureau Onderzoek & Innovatie of Santeon, the Netherlands, approved this study. The results will contribute to insight in and knowledge on the use of outcome data for SDM, and can stimulate sustainable implementation of SDM.
Trial registration number: NL8374, NL8375 and NL8376.

Gepubliceerd: BMJ Open. 2022;12(8):e055324.
Impact factor: 3.007; Q2

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11. A Potential Multimodal Test for Clinical Assessment of Visual Attention in Neurological Disorders
Barone V, van Dijk JP, Debeij-van Hall M, van Putten M.

Attention is an important aspect of human brain function and often affected in neurological disorders. Objective assessment of attention may assist in patient care, both for diagnostics and prognostication. We present a compact test using a combination of a choice reaction time task, eye-tracking and EEG for assessment of visual attention in the clinic. The system quantifies reaction time, parameters of eye movements (i.e. saccade metrics and fixations) and event related potentials (ERPs) in a single and fast (15 min) experimental design. We present pilot data from controls, patients with mild traumatic brain injury and epilepsy, to illustrate its potential use in assessing attention in neurological patients. Reaction times and eye metrics such as fixation duration, saccade duration and latency show significant differences ($p < .05$) between neurological patients and controls. Late ERP

components (200-800 ms) can be detected in the central line channels for all subjects, but no significant group differences could be found in the peak latencies and mean amplitudes. Our system has potential to assess key features of visual attention in the clinic. Pilot data show significant differences in reaction times and eye metrics between controls and patients, illustrating its promising use for diagnostics and prognostication.

Gepubliceerd: Clin EEG Neurosci. 2022:15500594221129962.
IMpact factor: 2.000; Q4

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12. Maximum entropy models provide functional connectivity estimates in neural networks
Lamberti M, Hess M, Dias I, van Putten M, le Feber J, Marzen S.

Tools to estimate brain connectivity offer the potential to enhance our understanding of brain functioning. The behavior of neuronal networks, including functional connectivity and induced connectivity changes by external stimuli, can be studied using models of cultured neurons. Cultured neurons tend to be active in groups, and pairs of neurons are said to be functionally connected when their firing patterns show significant synchronicity. Methods to infer functional connections are often based on pair-wise cross-correlation between activity patterns of (small groups of) neurons. However, these methods are not very sensitive to detect inhibitory connections, and they were not designed for use during stimulation. Maximum Entropy (MaxEnt) models may provide a conceptually different method to infer functional connectivity. They have the potential benefit to estimate functional connectivity during stimulation, and to infer excitatory as well as inhibitory connections. MaxEnt models do not involve pairwise comparison, but aim to capture probability distributions of sets of neurons that are synchronously active in discrete time bins. We used electrophysiological recordings from in vitro neuronal cultures on micro electrode arrays to investigate the ability of MaxEnt models to infer functional connectivity. Connectivity estimates provided by MaxEnt models correlated well with those obtained by conditional firing probabilities (CFP), an established cross-correlation based method. In addition, stimulus-induced connectivity changes were detected by MaxEnt models, and were of the same magnitude as those detected by CFP. Thus, MaxEnt models provide a potentially powerful new tool to study functional connectivity in neuronal networks.

Gepubliceerd: Sci Rep. 2022;12(1):9656.
Impact factor: 4.997 ; Q2

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13. National survey on the current practice and attitudes toward the management of chronic subdural hematoma
Holl DC, Blaauw J, Ista E, Dirven CMF, Kho KH, Jellema K, van der Gaag NA, Miah IP, den Hertog HM, van der Naalt J, Jacobs B, Verbaan D, Polinder S, Lingsma HF, Dammers R.

Background: Chronic subdural hematoma (CSDH) is a frequent pathological entity in daily clinical practice. However, evidence-based CSDH-guidelines are lacking and level I evidence from randomized clinical trials (RCTs) is limited. In order to establish and subsequently implement a guideline, insight into current clinical practice and attitudes toward CSDH-treatment is required. The aim is to explore current practice and attitudes toward CSDH-management in the Netherlands**.**
Methods: A national online survey was distributed among Dutch neurologists and neurosurgeons, examining variation in current CSDH-management through questions on treatment options, (peri)operative management, willingness to adopt new treatments and by presenting four CSDH-cases**.**

Results: One hundred nineteen full responses were received (8% of neurologists, N = 66 and 35% of neurosurgeons, N = 53). A majority of the respondents had a positive experience with burr-hole craniostomy (93%) and with a conservative policy (56%). Around a third had a positive experience with the use of dexamethasone as primary (30%) and additional (33.6%) treatment. These numbers were also reflected in the treatment preferences in the presented cases. (Peri)operative management corresponded among responding neurosurgeons. Most respondents would be willing to implement dexamethasone (98%) if equally effective as surgery and tranexamic acid (93%) if effective in CSDH-management**.**
Conclusion: Variation was found regarding preferential CSDH-treatment. However, this is considered not to be insurmountable when implementing evidence-based treatments. This baseline inventory on current clinical practice and current attitudes toward CSDH-treatment is a stepping-stone in the eventual development and implementation of a national guideline.

Gepubliceerd: Brain Behav. 2022;12(3):e2463.
Impact factor: 3.405; Q2

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14. Opinion & Special Article: Glioma Classification: How to Interpret Molecular Markers in a Diffuse Glioma Pathology Report
van der Meulen M, Ramos RC, Mason WP, Von Deimling A, Maas SLN.

Diffuse infiltrating gliomas are the most common malignant brain tumors in adults. The 2021 World Health Organization classification for central nervous system tumors (CNS5 WHO) has significantly altered the rules for classification and grading of diffuse gliomas. Clinicians, including neurology residents and neurologists, will have to consider the changes that include the introduction of new tumor types, allotting established tumor types to other groups, and substituting previously essential morphological features for additional molecular markers. For example, in the current classification, glioblastoma is defined as isocitrate dehydrogenase (IDH)-wildtype, grade 4. Whereas, a grade 4 IDH-mutated astrocytic glioma is referred to as astrocytoma, IDH-mutated, grade 4. Additionally, potential targeted treatments, based on the underlying molecular alterations, have become therapeutic options for diffuse gliomas. For clinicians, it is important to know the rationale for why these options are only available for specific tumors. Due to the emphasis of molecular markers in the CNS5 WHO classification, interpretation of a pathology report and understanding of its clinical implications can be challenging. This review describes the most important molecular alterations in glioma, summarizes the recent changes in the CNS5 WHO classification for glioma, and presents a stepwise approach for trainees and neurologist to decipher a glioma pathology report.

Gepubliceerd: Neurology. 2022.
Impact factor: 12.258; Q1

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15. External validation of prognostic models predicting outcome after chronic subdural hematoma
Holl DC, Mikolic A, Blaauw J, Lodewijkx R, Foppen M, Jellema K, van der Gaag NA, den Hertog HM, Jacobs B, van der Naalt J, Verbaan D, Kho KH, Dirven CMF, Dammers R, Lingsma HF, van Klaveren D.

Background: Several prognostic models for outcomes after chronic subdural hematoma (CSDH) treatment have been published in recent years. However, these models are not sufficiently validated for use in daily clinical practice. We aimed to assess the performance of existing prediction models for outcomes in patients diagnosed with CSDH**.**
Methods: We systematically searched relevant literature databases up to February 2021 to identify prognostic models for outcome prediction in patients diagnosed with CSDH. For the external

validation of prognostic models, we used a retrospective database, containing data of 2384 patients from three Dutch regions. Prognostic models were included if they predicted either mortality, hematoma recurrence, functional outcome, or quality of life. Models were excluded when predictors were absent in our database or available for < 150 patients in our database. We assessed calibration, and discrimination (quantified by the concordance index C) of the included prognostic models in our retrospective database**.**
Results: We identified 1680 original publications of which 1656 were excluded based on title or abstract, mostly because they did not concern CSDH or did not define a prognostic model. Out of 18 identified models, three could be externally validated in our retrospective database: a model for 30-day mortality in 1656 patients, a model for 2 months, and another for 3-month hematoma recurrence both in 1733 patients. The models overestimated the proportion of patients with these outcomes by 11% (15% predicted vs. 4% observed), 1% (10% vs. 9%), and 2% (11% vs. 9%), respectively. Their discriminative ability was poor to modest (C of 0.70 [0.63-0.77]; 0.46 [0.35-0.56]; 0.59 [0.51-0.66], respectively).
Conclusions: None of the examined models showed good predictive performance for outcomes after CSDH treatment in our dataset. This study confirms the difficulty in predicting outcomes after CSDH and emphasizes the heterogeneity of CSDH patients. The importance of developing high-quality models by using unified predictors and relevant outcome measures and appropriate modeling strategies is warranted.

Gepubliceerd: Acta Neurochir (Wien). 2022;164(10):2719-30.
Impact factor: 2.816 ; Q2

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16. Whole Exome Sequencing in Multi-Incident Families Identifies Novel Candidate Genes for Multiple Sclerosis
Horjus J, van Mourik-Banda T, Heerings MAP, Hakobjan M, De Witte W, Heersema DJ, Jansen AJ, Strijbis EMM, de Jong BA, Slettenaar AEJ, Zeinstra E, Hoogervorst ELJ, Franke B, Kruijer W, Jongen PJ, Visser LJ, Poelmans G.

Multiple sclerosis (MS) is a degenerative disease of the central nervous system in which auto-immunity-induced demyelination occurs. MS is thought to be caused by a complex interplay of environmental and genetic risk factors. While most genetic studies have focused on identifying common genetic variants for MS through genome-wide association studies, the objective of the present study was to identify rare genetic variants contributing to MS susceptibility. We used whole exome sequencing (WES) followed by co-segregation analyses in nine multi-incident families with two to four affected individuals. WES was performed in 31 family members with and without MS. After applying a suite of selection criteria, co-segregation analyses for a number of rare variants selected from the WES results were performed, adding 24 family members. This approach resulted in 12 exonic rare variants that showed acceptable co-segregation with MS within the nine families, implicating the genes MBP, PLK1, MECP2, MTMR7, TOX3, CPT1A, SORCS1, TRIM66, ITPR3, TTC28, CACNA1F, and PRAM1. Of these, three genes (MBP, MECP2, and CPT1A) have been previously reported as carrying MS-related rare variants. Six additional genes (MTMR7, TOX3, SORCS1, ITPR3, TTC28, and PRAM1) have also been implicated in MS through common genetic variants. The proteins encoded by all twelve genes containing rare variants interact in a molecular framework that points to biological processes involved in (de-/re-)myelination and auto-immunity. Our approach provides clues to possible molecular mechanisms underlying MS that should be studied further in cellular and/or animal models.

Gepubliceerd: Int J Mol Sci. 2022;23(19).
Impact factor: 4.730 ; Q1

17. Effect of metformin on outcome after acute ischemic stroke in patients with type 2 diabetes mellitus
Kersten C, Knottnerus ILH, Heijmans E, Haalboom M, Zandbergen AAM, den Hertog HM.

Introduction: Diabetes mellitus is a well-known risk factor for ischemic stroke and is associated with unfavorable outcome after stroke. Metformin is recommended as first-line treatment in these patients. Pre-stroke metformin use might have neuroprotective properties resulting in reduced stroke severity. However, results of the effects of pre-stroke metformin use on functional outcome are conflicting and has not been previously described in patients with type 2 diabetes mellitus regardless of stroke severity or revascularization treatment. In this study, we aimed to assess the association between metformin use and functional outcome in patients with type 2 diabetes mellitus and acute ischemic stroke**.**
Methods: We used data from patients with known type 2 diabetes mellitus who were admitted with acute ischemic stroke between 2017 and 2021 in the Isala Hospital Zwolle and Medisch Spectrum Twente (MST) Enschede, the Netherlands. The association between pre-stroke metformin use and favorable functional outcome at 3 months (defined as modified Rankin Scale (mRS) < 3) was expressed as Odds Ratios (ORs) with corresponding confidence intervals (CIs). Adjustments were made for age, sex, hyperglycemia on admission and revascularization treatment by means of multiple logistic regression**.**
Results: Nine hundred thirty seven patients were included of whom 592 patients (63%) used metformin. Six hundred seventy eight (74%) patients were hyperglycemic on admission. Median mRS was 3 (IQR 2-6) and 593 patients (63%) had a favorable outcome. Pre-stroke metformin use was associated with favorable outcome (aOR of 1.94 (95%- CI 1.45-2.59))**.**
Conclusion: In this study, we showed that pre-stroke metformin use was associated with favorable outcome after acute ischemic stroke in patients with diabetes mellitus type 2.

Gepubliceerd: J Stroke Cerebrovasc Dis. 2022;31(9):106648.
Impact factor: 2.677 ; Q3

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18. Association of hyperglycemia and computed tomographic perfusion deficits in patients who underwent endovascular treatment for acute ischemic stroke caused by a proximal intracranial occlusion: A subgroup analysis of a randomized phase 3 trial (MR CLEAN)
Kersten C, Zandbergen AAM, Berkhemer OA, Borst J, Haalboom M, Roos Y, Dippel DWJ, van Oostenbrugge RJ, van der Lugt A, van Zwam WH, Majoie CB, den Hertog HM.

Introduction: Hyperglycemia is highly prevalent in patients with acute ischemic stroke and is associated with increased risk of symptomatic intracranial hemorrhage, larger infarct size and unfavorable outcome. Furthermore, glucose may modify the effect of endovascular treatment (EVT) in patients with ischemic stroke. Hyperglycemia might lead to accelerated conversion of penumbra into infarct core. However, it remains uncertain whether hyperglycemia on admission is associated with the size of penumbra or infarct core in acute ischemic stroke. In this study, we aimed to assess the association between hyperglycemia and Computed Tomographic Perfusion (CTP) derived parameters in patients who underwent EVT for acute ischemic stroke**.**
Methods: We used data from the MR CLEAN study (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands). Hyperglycemia was defined as admission serum glucose of >7.8 mmol/L. Dichotomized and quantiles of glucose levels were related to size of core, penumbra and core penumbra ratio. Hypoperfused area is mean transient time 45% higher than that of the contralateral hemisphere. Core is the area with cerebral blood

volume of <2 mL/100 g and penumbra is the area with cerebral blood volume > 2 mL/100 g. Core-penumbra ratio is the ischemic core divided by the total volume of hypoperfused tissue (core plus penumbra) multiplied by 100. Adjustments were made for age, sex, NIHSS on admission, onset-imaging time and diabetes mellitus**.**
Results: Hundred seventy-three patients were included. Median glucose level on admission was 6.5 mmol/L (IQR 5.8-7.5 mmol/L) and thirty-five patients (20%) were hyperglycemic. Median core volume was 33.3 mL (IQR 13.6-62.4 mL), median penumbra volume was 80.2 mL (IQR 36.3-123.5 mL) and median core-penumbra ratio was 28.5% (IQR 18.6-45.8%). Patients with hyperglycemia on admission had larger core volumes and core penumbra ratio than normoglycemic patients with a regression coefficient of 15.1 (95% confidence interval (CI), 1.8 to 28.3) and 11.5 (95% confidence interval (CI), 3.4 to 19.7) respectively**.**
Conclusion: Hyperglycemia on admission was associated with larger ischemic core volume and larger core-penumbra ratio in patients with acute ischemic stroke who underwent endovascular treatment.

Gepubliceerd: J Neurol Sci. 2022;440:120333.
Impact factor: 4.553 ; Q2

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19. Diagnostic performance of an algorithm for automated large vessel occlusion detection on CT angiography
Luijten SPR, Wolff L, Duvekot MHC, van Doormaal PJ, Moudrous W, Kerkhoff H, Lycklama ANGJ, Bokkers RPH, Yo LSF, Hofmeijer J, van Zwam WH, van Es A, Dippel DWJ, Roozenbeek B, van der Lugt A, MR CLEAN Registry and PRESTO Investigators; Brouwers PJAM.

Background: Machine learning algorithms hold the potential to contribute to fast and accurate detection of large vessel occlusion (LVO) in patients with suspected acute ischemic stroke. We assessed the diagnostic performance of an automated LVO detection algorithm on CT angiography (CTA)**.**
Methods: Data from the MR CLEAN Registry and PRESTO were used including patients with and without LVO. CTA data were analyzed by the algorithm for detection and localization of LVO (intracranial internal carotid artery (ICA)/ICA terminus (ICA-T), M1, or M2). Assessments done by expert neuroradiologists were used as reference. Diagnostic performance was assessed for detection of LVO and per occlusion location by means of sensitivity, specificity, and area under the curve (AUC)**.**
Results: We analyzed CTAs of 1110 patients from the MR CLEAN Registry (median age (IQR) 71 years (60-80); 584 men; 1110 with LVO) and of 646 patients from PRESTO (median age (IQR) 73 years (62-82); 358 men; 141 with and 505 without LVO). For detection of LVO, the algorithm yielded a sensitivity of 89% in the MR CLEAN Registry and a sensitivity of 72%, specificity of 78%, and AUC of 0.75 in PRESTO. Sensitivity per occlusion location was 88% for ICA/ICA-T, 94% for M1, and 72% for M2 occlusion in the MR CLEAN Registry, and 80% for ICA/ICA-T, 95% for M1, and 49% for M2 occlusion in PRESTO**.**
Conclusion: The algorithm provided a high detection rate for proximal LVO, but performance varied significantly by occlusion location. Detection of M2 occlusion needs further improvement.

Gepubliceerd: J Neurointerv Surg. 2022;14(8):794-8.
Impact factor: 8.572 ; Q1

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20. Can we learn from hidden mistakes? Self-fulfilling prophecy and responsible neuroprognostic innovation
Mertens M, King OC, van Putten M, Boenink M.

A self-fulfilling prophecy (SFP) in neuroprognostication occurs when a patient in coma is predicted to have a poor outcome, and life-sustaining treatment is withdrawn on the basis of that prediction, thus directly bringing about a poor outcome (viz. death) for that patient. In contrast to the predominant emphasis in the bioethics literature, we look beyond the moral issues raised by the possibility that an erroneous prediction might lead to the death of a patient who otherwise would have lived. Instead, we focus on the problematic epistemic consequences of neuroprognostic SFPs in settings where research and practice intersect. When this sort of SFP occurs, the problem is that physicians and researchers are never in a position to notice whether their original prognosis was correct or incorrect, since the patient dies anyway. Thus, SFPs keep us from discerning false positives from true positives, inhibiting proper assessment of novel prognostic tests. This epistemic problem of SFPs thus impedes learning, but ethical obligations of patient care make it difficult to avoid SFPs. We then show how the impediment to catching false positive indicators of poor outcome distorts research on novel techniques for neuroprognostication, allowing biases to persist in prognostic tests. We finally highlight a particular risk that a precautionary bias towards early withdrawal of life-sustaining treatment may be amplified. We conclude with guidelines about how researchers can mitigate the epistemic problems of SFPs, to achieve more responsible innovation of neuroprognostication for patients in coma.

Gepubliceerd: J Med Ethics. 2022;48(11):922-8.
Impact factor: 5.926 ; Q1

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21. One EEG, one read - A manifesto towards reducing interrater variability among experts
Nascimento FA, Jing J, Beniczky S, Benbadis SR, Gavvala JR, Yacubian EMT, Wiebe S, Rampp S, van Putten M, Tripathi M, Cook MJ, Kaplan PW, Tatum WO, Trinka E, Cole AJ, Westover MB.

Gepubliceerd: Clin Neurophysiol. 2022;133:68-70.
Impact factor: 4.861; Q2

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22. Automated Scoring of Respiratory Events in Sleep With a Single Effort Belt and Deep Neural Networks
Nassi TE, Ganglberger W, Sun H, Bucklin AA, Biswal S, van Putten M, Thomas RJ, Westover MB.

Objective: Automatic detection and analysis of respiratory events in sleep using a single respiratoryeffort belt and deep learning**.**
Methods: Using 9,656 polysomnography recordings from the Massachusetts General Hospital (MGH), we trained a neural network (WaveNet) to detect obstructive apnea, central apnea, hypopnea and respiratory-effort related arousals. Performance evaluation included event-based analysis and apnea-hypopnea index (AHI) stratification. The model was further evaluated on a public dataset, the Sleep-Heart-Health-Study-1, containing 8,455 polysomnographic recordings**.**
Results: For binary apnea event detection in the MGH dataset, the neural network obtained a sensitivity of 68%, a specificity of 98%, a precision of 65%, a F1-score of 67%, and an area under the curve for the receiver operating characteristics curve and precision-recall curve of 0.93 and 0.71, respectively. AHI prediction resulted in a mean difference of 0.41 ± 7.8 and a r(2) of 0.90. For the multiclass task, we obtained varying performances: 84% of all labeled central apneas were correctly classified, whereas this metric was 51% for obstructive apneas, 40% for respiratory effort related arousals and 23% for hypopneas**.**
Conclusion: Our fully automated method can detect respiratory events and assess the AHI accurately. Differentiation of event types is more difficult and may reflect in part the complexity of human respiratory output and some degree of arbitrariness in the criteria used during manual

annotation. SIGNIFICANCE: The current gold standard of diagnosing sleep-disordered breathing, using polysomnography and manual analysis, is time-consuming, expensive, and only applicable in dedicated clinical environments. Automated analysis using a single effort belt signal overcomes these limitations.

Gepubliceerd: IEEE Trans Biomed Eng. 2022;69(6):2094-104.
Impact factor: 4.756 ; Q2

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23. Reply to "Letter regarding "Effects of targeted temperature management at 33 °C vs. 36 °C on comatose patients after cardiac arrest stratified by the severity of encephalopathy" by Lars W. Andersen, M.D., M.P.H., Ph.D., D.M.Sc. and Asger Granfeldt, M.D., Ph.D., D.M.Sc."
Nutma S, Hofmeijer J.

Gepubliceerd: Resuscitation. 2022;173:191.
Impact factor: 6.251 ; Q1

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24. Effects of targeted temperature management at 33 °C vs. 36 °C on comatose patients after cardiac arrest stratified by the severity of encephalopathy
Nutma S, Tjepkema-Cloostermans MC, Ruijter BJ, Tromp SC, van den Bergh WM, Foudraine NA, Kornips FHM, Drost G, Scholten E, Strang A, Beishuizen A, van Putten M, Hofmeijer J.

Objectives: To assess neurological outcome after targeted temperature management (TTM) at 33 °C vs. 36 °C, stratified by the severity of encephalopathy based on EEG-patterns at 12 and 24 h.
Design: Post hoc analysis of prospective cohort study. SETTING: Five Dutch Intensive Care units**.**
Patients: 479 adult comatose post-cardiac arrest patients**.**
Interventions: TTM at 33 °C (n = 270) or 36 °C (n = 209) and continuous EEG monitoring**.**
measurements and Main Results: Outcome according to the cerebral performance category (CPC) score at 6 months post-cardiac arrest was similar after 33 °C and 36 °C. However, when stratified by the severity of encephalopathy based on EEG-patterns at 12 and 24 h after cardiac arrest, the proportion of good outcome (CPC 1-2) in patients with moderate encephalopathy was significantly larger after TTM at 33 °C (66% vs. 45%; Odds Ratios 2.38, 95% CI = 1.32-4.30; p = 0.004). In contrast, with mild encephalopathy, there was no statistically significant difference in the proportion of patients with good outcome between 33 °C and 36 °C (88% vs. 81%; OR 1.68, 95% CI = 0.65-4.38; p = 0.282). Ordinal regression analysis showed a shift towards higher CPC scores when treated with TTM 33 °C as compared with 36 °C in moderate encephalopathy (cOR 2.39; 95% CI = 1.40-4.08; p = 0.001), but not in mild encephalopathy (cOR 0.81 95% CI = 0.41-1.59; p = 0.537). Adjustment for initial cardiac rhythm and cause of arrest did not change this relationship.
Conclusions: Effects of TTM probably depend on the severity of encephalopathy in comatose patients after cardiac arrest. These results support inclusion of predefined subgroup analyses based on EEG measures of the severity of encephalopathy in future clinical trials.

Gepubliceerd: Resuscitation. 2022;173:147-53.
Impact factor: 6.251 ; Q1

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25. SARS-CoV-2 vaccine-related neurological complications
Oonk NGM, Ettema AR, van Berghem H, de Klerk JJ, van der Vegt JPM, van der Meulen M.

Objective: To describe three cases with neurological symptoms after SARS-CoV-2 vaccination**.**

Methods: A case series followed by a review of the literature, describing hypotheses on how neurological symptoms might develop after vaccination**.**
Results: The different temporal relationship between the onset or worsening of different neurological symptoms suggests different pathophysiological mechanisms. Progression of post-infectious myoclonus, caused by a previous SARS-CoV-2-infection, shortly after vaccination suggests a renewed auto-immune mediated crossreaction of antibodies to both viral epitopes and central nervous system components. Thunderclap headache after vaccination suggests a similar pathophysiological mechanism to the headache and other flu-like symptoms described after vaccination against other viruses. This might be ascribed to the activation of immunoinflammatory mediators or accompanying fever. Although headache accompanied by encephalopathy and focal neurological deficit might occur as part of a cytokine release syndrome, this is clinically less likely.
Conclusions: A variety of symptoms, including thunderclap headache, focal deficits and movement disorders, can occur after SARS-CoV-2 vaccination, and an activation or reactivation of the immune system is suggested as most likely cause. However, one should be careful about claiming a direct correlation. It remains important to exclude other causes, such as structural lesions, infections or subarachnoid hemorrhage, and future research is required to understand possible pathophysiological mechanisms and associations with the SARS-CoV-2 vaccine.

Gepubliceerd: Neurol Sci. 2022;43(4):2295-7.
Impact factor: 3.830 ; Q2

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26. The Effect of a Structured Medication Review on Quality of Life in Parkinson's Disease
Oonk NGM, Movig KLL, van der Palen J, Nibourg SAF, Koehorst-Ter Huurne K, Nijmeijer HW, van Kesteren ME, Dorresteijn LDA.

Background: Drug therapy is important for controlling symptoms in Parkinson's disease (PD). However, it often results in complex medication regimens and could easily lead to drug related problems (DRP), suboptimal adherence and reduced treatment efficacy. A structured medication review (SMR) could address these issues and optimize therapy, although little is known about clinical effects in PD patients.
Objective: To analyze whether an SMR improves quality of life (QoL) in PD**.**
Methods: In this multicenter randomized controlled trial, half of the 202 PD patients with polypharmacy received a community pharmacist-led SMR. The control group received usual care. Assessments at baseline, and after three and six months comprised six validated questionnaires. Primary outcome was PD specific QoL [(PDQ-39; range 0 (best QoL) - 100 (worst QoL)]. Secondary outcomes were disability score, non-motor symptoms, general health status, and personal care giver's QoL. Furthermore, DRPs, proposed interventions, and implemented modifications in medication schedules were analyzed**.**
Results: No improvement in QoL was seen six months after an SMR, with a non-significant treatment effect difference of 2.09 (-0.63;4.80) in favor of the control group. No differences were found in secondary outcomes. In total, 260 potential DRPs were identified (2.6 (±1.8) per patient), of which 62% led to drug therapy optimization**.**
Conclusion: In the current setting, a community pharmacist-led SMR did not improve QoL in PD patients, nor improved other pre-specified outcomes.

Gepubliceerd: J Parkinsons Dis. 2022;12(4):1295-306.
Impact factor: 5.520 ; Q2

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27. Outcome Prediction of Postanoxic Coma: A Comparison of Automated Electroencephalography Analysis Methods

Pham SDT, Keijzer HM, Ruijter BJ, Seeber AA, Scholten E, Drost G, van den Bergh WM, Kornips FHM, Foudraine NA, Beishuizen A, Blans MJ, Hofmeijer J, van Putten M, Tjepkema-Cloostermans MC.

Background: To compare three computer-assisted quantitative electroencephalography (EEG) prediction models for the outcome prediction of comatose patients after cardiac arrest regarding predictive performance and robustness to artifacts**.**
Methods: A total of 871 continuous EEGs recorded up to 3 days after cardiac arrest in intensive care units of five teaching hospitals in the Netherlands were retrospectively analyzed. Outcome at 6 months was dichotomized as "good" (Cerebral Performance Category 1-2) or "poor" (Cerebral Performance Category 3-5). Three prediction models were implemented: a logistic regression model using two quantitative features, a random forest model with nine features, and a deep learning model based on a convolutional neural network. Data from two centers were used for training and fivefold cross-validation (n = 663), and data from three other centers were used for external validation (n = 208). Model output was the probability of good outcome. Predictive performances were evaluated by using receiver operating characteristic analysis and the calculation of predictive values. Robustness to artifacts was evaluated by using an artifact rejection algorithm, manually added noise, and randomly flattened channels in the EEG**.**
Results: The deep learning network showed the best overall predictive performance. On the external test set, poor outcome could be predicted by the deep learning network at 24 h with a sensitivity of 54% (95% confidence interval [CI] 44-64%) at a false positive rate (FPR) of 0% (95% CI 0-2%), significantly higher than the logistic regression (sensitivity 33%, FPR 0%) and random forest models (sensitivity 13%, FPR, 0%) ($p < 0.05$). Good outcome at 12 h could be predicted by the deep learning network with a sensitivity of 78% (95% CI 52-100%) at a FPR of 12% (95% CI 0-24%) and by the logistic regression model with a sensitivity of 83% (95% CI 83-83%) at a FPR of 3% (95% CI 3-3%), both significantly higher than the random forest model (sensitivity 1%, FPR 0%) ($p < 0.05$). The results of the deep learning network were the least affected by the presence of artifacts, added white noise, and flat EEG channels.
Conclusions: A deep learning model outperformed logistic regression and random forest models for reliable, robust, EEG-based outcome prediction of comatose patients after cardiac arrest.

Gepubliceerd: Neurocrit Care. 2022;37(Suppl 2):248-58.
Impact factor: 3.532 ; Q2

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28. Etiology of Large Vessel Occlusion Posterior Circulation Stroke: Results of the MR CLEAN Registry

Pirson F, Boodt N, Brouwer J, Bruggeman AAE, Hinsenveld WH, Staals J, van Zwam WH, van der Leij C, Brans RJB, Majoie C, Dippel DWJ, van der Lugt A, Schonewille WJ, van Oostenbrugge RJ, MR CLEAN Registry Investigators; Brouwers PJAM.

Background: In patients with large vessel occlusion stroke of the anterior circulation, underlying cause is a determinant of outcome. Whether this is the case for posterior circulation large vessel occlusion stroke has yet to be determined. We aimed to report on cause in patients with posterior circulation stroke treated with endovascular thrombectomy and to analyze the association with functional outcome**.**
Methods: We used data of patients with posterior circulation stroke included in the MR CLEAN (Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) registry, a prospective multicenter observational study, between 2014 and 2018. Stroke cause was categorized into large artery atherosclerosis (LAA), cardioembolism, arterial dissection,

embolic stroke of undetermined source (ESUS), other determined cause, or undetermined cause. For primary analysis on the association between cause and outcome, we used multivariable ordinal logistic regression analysis to estimate the adjusted common odds ratio for a shift towards a better functional outcome on the modified Rankin Scale at 90 days with LAA as a reference group. Secondary outcomes included favorable functional outcome (modified Rankin Scale score 0-3), National Institutes of Health Stroke Scale score at 24 to 48 hours, reperfusion on digital subtraction angiography, and stroke progression.
Results: Of 264 patients with posterior circulation stroke, 84 (32%) had LAA, 48 (18%) cardioembolism, 31 (12%) dissection, and 14 (5%) ESUS. Patients with a dissection were younger (48 [interquartile range, 43-60] years) and had a lower National Institutes of Health Stroke Scale at baseline (12 [interquartile range, 6-31]) than patients with other cause. Functional outcome was better for patients with cardioembolism and ESUS compared to LAA (modified Rankin Scale adjusted common odds ratio, 2.4 [95% CI, 1.1-5.2], respectively adjusted common odds ratio, 3.1 [95% CI, 1.0-9.3]). Patients with a dissection had a lower chance of successful reperfusion compared with LAA (adjusted odds ratio, 0.20 [95% CI, 0.06-0.70]).
Conclusions: Unlike the anterior circulation, most frequent cause in our posterior large vessel occlusion stroke cohort is LAA followed by cardioembolism, dissection, and ESUS. Patients with cardioembolism and ESUS have a better prognosis for functional outcome after endovascular thrombectomy than patients with LAA.

Gepubliceerd: Stroke. 2022;53(8):2468-77.
Impact factor: 10.170 ; Q1

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29. Endovascular Treatment for Posterior Circulation Stroke in Routine Clinical Practice: Results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands Registry

Pirson FAV, Boodt N, Brouwer J, Bruggeman AAE, den Hartog SJ, Goldhoorn RB, Langezaal LCM, Staals J, van Zwam WH, van der Leij C, Brans RJB, Majoie C, Coutinho JM, Emmer BJ, Dippel DWJ, van der Lugt A, Vos JA, van Oostenbrugge RJ, Schonewille WJ, MR CLEAN Registry Investigators; Brouwers PJAM.

Background and Purpose: The benefit of endovascular treatment (EVT) for posterior circulation stroke (PCS) remains uncertain, and little is known on treatment outcomes in clinical practice. This study evaluates outcomes of a large PCS cohort treated with EVT in clinical practice. Simultaneous to this observational study, several intervention centers participated in the BASICS trial (Basilar Artery International Cooperation Study), which tested the efficacy of EVT for basilar artery occlusion in a randomized setting. We additionally compared characteristics and outcomes of patients treated outside BASICS in trial centers to those from nontrial centers.
Methods: We included patients with PCS from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands Registry: a prospective, multicenter, observational study of patients who underwent EVT in the Netherlands between 2014 and 2018. Primary outcome was a score of 0 to 3 on the modified Rankin Scale at 90 days. Secondary outcomes included reperfusion status and symptomatic intracranial hemorrhage. For outcome comparison between patients treated in trial versus nontrial centers, we used ordinal logistic regression analysis.
Results: We included 264 patients of whom 135 (51%) had received intravenous thrombolysis. The basilar artery was most often involved (77%). Favorable outcome (modified Rankin Scale score 0-3) was observed in 115/252 (46%) patients, and 109/252 (43%) patients died. Successful reperfusion was achieved in 178/238 (75%), and symptomatic intracranial hemorrhage occurred in 9/264 (3%). The 154 nontrial patients receiving EVT in BASICS trial centers had similar characteristics and

outcomes as the 110 patients treated in nontrial centers (modified Rankin Scale adjusted cOR: 0.77 [95% CI, 0.5-1.2]).
Conclusions: Our study shows that high rates of favorable clinical outcome and successful reperfusion can be achieved with EVT for PCS, despite high mortality. Characteristics and outcomes of patients treated in trial versus nontrial centers were similar indicating that our cohort is representative of clinical practice in the Netherlands. Randomized studies using modern treatment approaches are needed for further insight in the benefit of EVT for PCS.

Gepubliceerd: Stroke. 2022;53(3):758-68.
Impact factor: 10.170 ; Q1

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30. Development of a patient decision aid for discharge planning of hospitalized patients with stroke
Prick JCM, van Schaik SM, Deijle IA, Dahmen R, Brouwers P, Hilkens PHE, Garvelink MM, Engels N, Ankersmid JW, Keus SHJ, The R, Takahashi A, van Uden-Kraan CF, van der Wees PJ, Van den Berg-Vos RM.

Background: Patient involvement in discharge planning of patients with stroke can be accomplished by providing personalized outcome information and promoting shared decision-making. The aim of this study was to develop a patient decision aid (PtDA) for discharge planning of hospitalized patients with stroke**.**
Methods: A convergent mixed methods design was used, starting with needs assessments among patients with stroke and health care professionals (HCPs). Results of these assessments were used to develop the PtDA with integrated outcome information in several co-creation sessions. Subsequently, acceptability and usability were tested to optimize the PtDA. Development was guided by the International Patient Decision Aids Standards (IPDAS) criteria**.**
Results: In total, 74 patients and 111 HCPs participated in this study. A three-component PtDA was developed, consisting of: 1) a printed consultation sheet to introduce the options for discharge destinations, containing information that can be specified for each individual patient; 2) an online information and deliberation tool to support patient education and clarification of patient values, containing an integrated "patients-like-me" model with outcome information about discharge destinations; 3) a summary sheet to support actual decision-making during consultation, containing the patient's values and preferences concerning discharge planning. In the acceptability test, all qualifying and certifying IPDAS criteria were fulfilled. The usability test showed that patients and HCPs highly appreciated the PtDA with integrated outcome information.
Conclusions: The developed PtDA was found acceptable and usable by patients and HCPs and is currently under investigation in a clinical trial to determine its effectiveness.

Gepubliceerd: BMC Neurol. 2022;22(1):245.
Impact factor: 2.903 ; Q3

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31. Experiences with information provision and preferences for decision making of patients with acute stroke
Prick JCM, Zonjee VJ, van Schaik SM, Dahmen R, Garvelink MM, Brouwers P, Saxena R, Keus SHJ, Deijle IA, van Uden-Kraan CF, van der Wees PJ, Van den Berg-Vos RM.

Objective: The aim of this study was to gain insight into experiences of patients with acute stroke regarding information provision and their preferred involvement in decision-making processes during the initial period of hospitalisation**.**

Methods: A sequential explanatory design was used in two independent cohorts of patients with stroke, starting with a survey after discharge from hospital (cohort 1) followed by observations and structured interviews during hospitalisation (cohort 2). Quantitative data were analysed descriptively**.**
Results: In total, 72 patients participated in this study (52 in cohort 1 and 20 in cohort 2). During hospitalisation, the majority of the patients were educated about acute stroke and their treatment. Approximately half of the patients preferred to have an active role in the decision-making process, whereas only 21% reported to be actively involved. In cohort 2, 60% of the patients considered themselves capable to carefully consider treatment options.
Conclusions: Active involvement in the acute decision-making process is preferred by approximately half of the patients with acute stroke and most of them consider themselves capable of doing so. However, they experience a limited degree of actual involvement. PRACTICE IMPLICATIONS: Physicians can facilitate patient engagement by explicitly emphasising when a decision has to be made in which the patient's opinion is important.

Gepubliceerd: Patient Educ Couns. 2022;105(5):1123-9.
Impact factor: 3.467 ; Q1

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32. Effect of Intravenous Alteplase Treatment on First-Line Stent Retriever Versus Aspiration Alone During Endovascular Treatment
Rinkel LA, Treurniet KM, Nieboer D, Kappelhof M, LeCouffe NE, Bruggeman AAE, van Zwam WH, Lycklama ANGJ, Ghariq E, Uyttenboogaart M, Dippel DWJ, Roos Y, Coutinho JM, Majoie C, Emmer BJ, MR CLEAN-NO IV Investigators; Brouwers PJAM.

Background: We aimed to assess whether the effect of intravenous alteplase treatment (IVT) before endovascular treatment (EVT) on outcome is modified by first-line technique during EVT in IVT eligible patients**.**
Methods: This was a post hoc analysis from MR CLEAN-NO IV (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands - Intravenous Treatment Followed by Intra-Arterial Treatment Versus Direct Intra-Arterial Treatment for Acute Ischemic Stroke Caused by a Proximal Intracranial Occlusion), a randomized trial of IVT followed by EVT versus EVT alone in patients presenting directly to EVT-capable centers. We included data from all patients who underwent EVT with a thrombectomy attempt. We compared patients treated with stent retriever (with or without aspiration) to aspiration alone as first-line EVT technique and assessed the interaction of first-line EVT technique with IVT treatment. Primary outcome was the 90-day modified Rankin Scale score, analyzed with mixed model ordinal regression for a shift towards better outcome. Secondary outcomes included successful reperfusion (extended Thrombolysis in Cerebral Infarction score 2b-3)**.**
Results: Of 473 included patients, 102 (21.6%) were treated with aspiration alone as first-line technique. In the full population, functional outcome was similar for patients treated with stent retriever versus aspiration only (adjusted common odds ratio [acOR]' 1.07 [95% CI, 0.69-1.66]). We observed a significant interaction between IVT and first-line EVT technique (P=0.03). In the aspiration-only group, patients treated with EVT alone had worse functional outcome compared to those treated with IVT and EVT (acOR, 0.44 [95% CI, 0.21-0.90]). In the stent retriever group, functional outcome did not differ between patients treated with or without IVT (acOR, 1.08 [95% CI, 0.74-1.57]). There was no statistically significant interaction for successful reperfusion.
Conclusions: In MR CLEAN-NO IV, the treatment effect of IVT was modified by first-line EVT technique. Patients treated with aspiration only as first-line technique had worse clinical outcomes if they did not receive IVT. No such difference was observed in patients treated with stent retrievers. Confirmation by pooling with results from other trials is needed to confirm these findings.

Gepubliceerd: Stroke. 2022;53(11):3278-88.
Impact factor: 10.170 ; Q1

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33. Transcranial magnetic stimulation as biomarker of excitability in drug development: A randomized, double-blind, placebo-controlled, cross-over study
Ruijs TQ, Heuberger J, de Goede AA, Ziagkos D, Otto ME, Doll RJ, van Putten M, Groeneveld GJ.

Aims: The purpose of this study was to investigate pharmacodynamic effects of drugs targeting cortical excitability using transcranial magnetic stimulation (TMS) combined with electromyography (EMG) and electroencephalography (EEG) in healthy subjects, to further develop TMS outcomes as biomarkers for proof-of-mechanism in early-phase clinical drug development. Antiepileptic drugs presumably modulate cortical excitability. Therefore, we studied effects of levetiracetam, valproic acid and lorazepam on cortical excitability in a double-blind, placebo-controlled, 4-way cross-over study**.**
Methods: In 16 healthy male subjects, single- and paired-pulse TMS-EMG-EEG measurements were performed predose and 1.5, 7 and 24 hours postdose. Treatment effects on motor-evoked potential, short and long intracortical inhibition and TMS-evoked potential amplitudes, were analysed using a mixed model ANCOVA and cluster-based permutation analysis**.**
Results: We show that motor-evoked potential amplitudes decreased after administration of levetiracetam (estimated difference [ED] -378.4 μV; 95%CI: -644.3, -112.5 μV; P < .01), valproic acid (ED -268.8 μV; 95%CI: -532.9, -4.6 μV; P = .047) and lorazepam (ED -330.7 μV; 95%CI: -595.6, -65.8 μV; P = .02) when compared with placebo. Long intracortical inhibition was enhanced by levetiracetam (ED -60.3%; 95%CI: -87.1%, -33.5%; P < .001) and lorazepam (ED -68.2%; 95%CI: -94.7%, -41.7%; P < .001) at a 50-ms interstimulus interval. Levetiracetam increased TMS-evoked potential component N45 (P = .004) in a central cluster and decreased N100 (P < .001) in a contralateral cluster**.**
Conclusion: This study shows that levetiracetam, valproic acid and lorazepam decrease cortical excitability, which can be detected using TMS-EMG-EEG in healthy subjects. These findings provide support for the use of TMS excitability measures as biomarkers to demonstrate pharmacodynamic effects of drugs that influence cortical excitability.

Gepubliceerd: Br J Clin Pharmacol. 2022;88(6):2926-37.
Impact factor: 3.716; Q2

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34. Spinal Cord Stimulation and Urinary Dysfunction
Smeijers S, Kho KH, De Vlieger J, Van Hoylandt A, Nuttin B, Theys T.

Gepubliceerd: Pain Med. 2022;23(7):1204-11.
Impact factor: 3.637 ; Q2

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35. Impaired Visual Emotion Recognition After Minor Ischemic Stroke
Smith-Spijkerboer W, Meeske K, van der Palen JAM, den Hertog HM, Smeets-Schouten AS, van Hout M, Dorresteijn LDA.

Objective: To assess the prevalence of impaired visual emotion recognition in patients who have experienced a minor ischemic stroke in the subacute phase and to determine associated factors of impaired visual emotion recognition.

Design:A prospective observational study. SETTING: Stroke unit of a teaching hospital. PARTICIPANTS: Patients with minor ischemic stroke (N=112)**.**
Interventions: Not applicable. MAIN OUTCOME MEASURES: Patients with minor stroke underwent a neuropsychological assessment in the subacute phase for visual emotion recognition by the Ekman 60 Faces Test and for general cognition. Univariable linear regression analyses were performed to identify associated factors of emotion recognition impairment**.**
Results: In 112 minor stroke patients, we found a prevalence of 25% of impaired visual emotion recognition. This was significantly correlated with impaired general cognition. Nevertheless, 10.9% of patients with normal general cognition still had impaired emotion recognition. Mood was negatively associated. Stroke localization, hemisphere side, and sex were not associated**.**
Conclusion: Impaired visual emotion recognition is found in about one-quarter of patients with minor ischemic stroke.

Gepubliceerd: Arch Phys Med Rehabil. 2022;103(5):958-63.
Impact factor: 4.060 ; Q1

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36. The Association between Hypoxia-Induced Low Activity and Apoptosis Strongly Resembles That between TTX-Induced Silencing and Apoptosis
Taxis di Bordonia EVD, Hassink GC, Levers MR, Frega M, Hofmeijer J, van Putten M, le Feber J.

In the penumbra of a brain infarct, neurons initially remain structurally intact, but perfusion is insufficient to maintain neuronal activity at physiological levels. Improving neuronal recovery in the penumbra has large potential to advance recovery of stroke patients, but penumbral pathology is incompletely understood, and treatments are scarce. We hypothesize that low activity in the penumbra is associated with apoptosis and thus contributes to irreversible neuronal damage. We explored the putative relationship between low neuronal activity and apoptosis in cultured neurons exposed to variable durations of hypoxia or TTX. We combined electrophysiology and live apoptosis staining in 42 cultures, and compared effects of hypoxia and TTX silencing in terms of network activity and apoptosis. Hypoxia rapidly reduced network activity, but cultures showed limited apoptosis during the first 12 h. After 24 h, widespread apoptosis had occurred. This was associated with full activity recovery observed upon reoxygenation within 12 h, but not after 24 h. Similarly, TTX exposure strongly reduced activity, with full recovery upon washout within 12 h, but not after 24 h. Mean temporal evolution of apoptosis in TTX-treated cultures was the same as in hypoxic cultures. These results suggest that prolonged low activity may be a common factor in the pathways towards apoptosis.

Gepubliceerd: Int J Mol Sci. 2022;23(5).
Impact factor: 4.730 ; Q1

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37. Predictors of poor outcome despite successful endovascular treatment for ischemic stroke: results from the MR CLEAN Registry
van de Graaf RA, Samuels N, Chalos V, Lycklama ANGJ, van Beusekom H, Yoo AJ, van Zwam WH, Majoie C, Roos Y, van Doormaal PJ, Ben Hassen W, van der Lugt A, Dippel DWJ, Lingsma HF, van Es A, Roozenbeek B, MR CLEAN Registry investigators; Brouwers, PJAM.

Background: Approximately one-third of patients with ischemic stroke treated with endovascular treatment do not recover to functional independence despite rapid and successful recanalization. We aimed to quantify the importance of predictors of poor functional outcome despite successful reperfusion**.**

Methods: We analyzed patients from the MR CLEAN Registry between March 2014 and November 2017 with successful reperfusion (extended Thrombolysis In Cerebral Infarction ≥2B). First, predictors were selected based on expert opinion and were clustered according to acquisition over time (ie, baseline patient factors, imaging factors, treatment factors, and postprocedural factors). Second, several models were constructed to predict 90-day functional outcome (modified Rankin Scale (mRS)). The relative importance of individual predictors in the most extensive model was expressed by the proportion of unique added χ(2) to the model of that individual predictor**.**
Results: Of 3180 patients, 1913 (60%) had successful reperfusion. Of these 1913 patients, 1046 (55%) were functionally dependent at 90 days (mRS >2). The most important predictors for mRS were baseline patient factors (ie, pre-stroke mRS, added χ(2) 0.16; National Institutes of Health Stroke Scale score at baseline, added χ(2) 0.12; age, added χ(2) 0.10), and postprocedural factors (ie, symptomatic intracranial hemorrhage (sICH), added χ(2) 0.12; pneumonia, added χ(2) 0.09). The probability of functional independence for a typical stroke patient with sICH was 54% (95% CI 36% to 72%) lower compared with no sICH, and 21% (95% CI 4% to 38%) for pneumonia compared with no pneumonia**.**
Conclusion: Baseline patient factors and postprocedural adverse events are important predictors of poor functional outcome in successfully reperfused patients with ischemic stroke. This implies that prevention of postprocedural adverse events has the greatest potential to further improve outcomes in these patients.

Gepubliceerd: J Neurointerv Surg. 2022;14(7):660-5.
Impact factor: 8.572 ; Q1

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38. First-line chemotherapeutic treatment for oligodendroglioma, WHO grade 3-PCV or temozolomide?
van der Meulen M, Mason WP.

Gepubliceerd: Neurooncol Pract. 2022;9(3):163-4.
Impact factor: 0 ; Q NVT

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39. Safety and efficacy of aspirin, unfractionated heparin, both, or neither during endovascular stroke treatment (MR CLEAN-MED): an open-label, multicentre, randomised controlled trial
van der Steen W, van de Graaf RA, Chalos V, Lingsma HF, van Doormaal PJ, Coutinho JM, Emmer BJ, de Ridder I, van Zwam W, van der Worp HB, van der Schaaf I, Gons RAR, Yo LSF, Boiten J, van den Wijngaard I, Hofmeijer J, Martens J, Schonewille W, Vos JA, Tuladhar AM, de Laat KF, van Hasselt B, Remmers M, Vos D, Rozeman A, Elgersma O, Uyttenboogaart M, Bokkers RPH, van Tuijl J, Boukrab I, van den Berg R, Beenen LFM, Roosendaal SD, Postma AA, Krietemeijer M, Lycklama G, Meijer FJA, Hammer S, van der Hoorn A, Yoo AJ, Gerrits D, Truijman MTB, Zinkstok S, Koudstaal PJ, Manschot S, Kerkhoff H, Nieboer D, Berkhemer O, Wolff L, van der Sluijs PM, van Voorst H, Tolhuisen M, Roos Y, Majoie C, Staals J, van Oostenbrugge RJ, Jenniskens SFM, van Dijk LC, den Hertog HM, van Es A, van der Lugt A, Dippel DWJ, Roozenbeek B, MR CLEAN-MED investigators; Brouwers, PJAM.

Background: Aspirin and unfractionated heparin are often used during endovascular stroke treatment to improve reperfusion and outcomes. However, the effects and risks of anti-thrombotics for this indication are unknown. We therefore aimed to assess the safety and efficacy of intravenous aspirin, unfractionated heparin, both, or neither started during endovascular treatment in patients with ischaemic stroke**.**
Methods: We did an open-label, multicentre, randomised controlled trial with a 2 × 3 factorial design in 15 centres in the Netherlands. We enrolled adult patients (ie, ≥18 years) with ischaemic stroke due

to an intracranial large-vessel occlusion in the anterior circulation in whom endovascular treatment could be initiated within 6 h of symptom onset. Eligible patients had a score of 2 or more on the National Institutes of Health Stroke Scale, and a CT or MRI ruling out intracranial haemorrhage. Randomisation was done using a web-based procedure with permuted blocks and stratified by centre. Patients were randomly assigned (1:1) to receive either periprocedural intravenous aspirin (300 mg bolus) or no aspirin, and randomly assigned (1:1:1) to receive moderate-dose unfractionated heparin (5000 IU bolus followed by 1250 IU/h for 6 h), low-dose unfractionated heparin (5000 IU bolus followed by 500 IU/h for 6 h), or no unfractionated heparin. The primary outcome was the score on the modified Rankin Scale at 90 days. Symptomatic intracranial haemorrhage was the main safety outcome. Analyses were based on intention to treat, and treatment effects were expressed as odds ratios (ORs) or common ORs, with adjustment for baseline prognostic factors. This trial is registered with the International Standard Randomised Controlled Trial Number, ISRCTN76741621**.**
Findings: Between Jan 22, 2018, and Jan 27, 2021, we randomly assigned 663 patients; of whom, 628 (95%) provided deferred consent or died before consent could be asked and were included in the modified intention-to-treat population. On Feb 4, 2021, after unblinding and analysis of the data, the trial steering committee permanently stopped patient recruitment and the trial was stopped for safety concerns. The risk of symptomatic intracranial haemorrhage was higher in patients allocated to receive aspirin than in those not receiving aspirin (43 [14%] of 310 vs 23 [7%] of 318; adjusted OR 1·95 [95% CI 1·13-3·35]) as well as in patients allocated to receive unfractionated heparin than in those not receiving unfractionated heparin (44 [13%] of 332 vs 22 [7%] of 296; 1·98 [1·14-3·46]). Both aspirin (adjusted common OR 0·91 [95% CI 0·69-1·21]) and unfractionated heparin (0·81 [0·61-1·08]) led to a non-significant shift towards worse modified Rankin Scale scores.
Interpretation: Periprocedural intravenous aspirin and unfractionated heparin during endovascular stroke treatment are both associated with an increased risk of symptomatic intracranial haemorrhage without evidence for a beneficial effect on functional outcome. FUNDING: The Collaboration for New Treatments of Acute Stroke consortium, the Brain Foundation Netherlands, the Ministry of Economic Affairs, Stryker, Medtronic, Cerenovus, and the Dutch Heart Foundation.

Gepubliceerd: Lancet. 2022;399(10329):1059-69.
Impact factor: 202.731 ; Q1

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40. Determinants of Symptomatic Intracranial Hemorrhage After Endovascular Stroke Treatment: A Retrospective Cohort Study

van der Steen W, van der Ende NAM, van Kranendonk KR, Chalos V, van Oostenbrugge RJ, van Zwam WH, Roos Y, van Doormaal PJ, van Es A, Lingsma HF, Majoie C, van der Lugt A, Dippel DWJ, Roozenbeek B, MR CLEAN Trial and MR CLEAN Registry Investigators; Brouwers PJAM.

Background: Symptomatic intracranial hemorrhage (sICH) is a serious complication after endovascular treatment for ischemic stroke. We aimed to identify determinants of its occurrence and location**.**
Methods: We retrospectively analyzed data from the Dutch MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) and MR CLEAN registry. We included adult patients with a large vessel occlusion in the anterior circulation who underwent endovascular treatment within 6.5 hours of stroke onset. We used univariable and multivariable logistic regression analyses to identify determinants of overall sICH occurrence, sICH within infarcted brain tissue, and sICH outside infarcted brain tissue**.**
Results: SICH occurred in 203 (6%) of 3313 included patients and was located within infarcted brain tissue in 50 (25%), outside infarcted brain tissue in 23 (11%), and both within and outside infarcted brain tissue in 116 (57%) patients. In 14 patients (7%), data on location were missing. Prior antiplatelet use, baseline systolic blood pressure, baseline plasma glucose levels, post-endovascular

treatment modified treatment in cerebral ischemia score, and duration of procedure were associated with all outcome parameters. In addition, determinants of sICH within infarcted brain tissue included history of myocardial infarction (adjusted odds ratio, 1.65 [95% CI, 1.06-2.56]) and poor collateral score (adjusted odds ratio, 1.42 [95% CI, 1.02-1.95]), whereas determinants of sICH outside infarcted brain tissue included level of occlusion on computed tomography angiography (internal carotid artery or internal carotid artery terminus compared with M1: adjusted odds ratio, 1.79 [95% CI, 1.16-2.78]).
Conclusions: Several factors, some potentially modifiable, are associated with sICH occurrence. Further studies should investigate whether modification of baseline systolic blood pressure or plasma glucose level could reduce the risk of sICH. In addition, determinants differ per location of sICH, supporting the hypothesis of varying underlying mechanisms. REGISTRATION: URL: https://www.isrctn.com/;
Unique identifier: ISRCTN10888758.

Gepubliceerd: Stroke. 2022;53(9):2818-27.
Impact factor: 10.170 ; Q1

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41. The Montreal Cognitive Assessment is a valid cognitive screening tool for cardiac arrest survivors
van Gils P, van Heugten C, Hofmeijer J, Keijzer H, Nutma S, Duits A.

Aim: The survival rate of out-of-hospital cardiac arrest (OHCA) patients has increased over the past decades. This gives rise to a growing number of patients with hypoxic-ischemic brain damage and cognitive impairment. Currently, cognitive impairment is underdiagnosed in OHCA patients. There is a need for a validated cognitive screening instrument to identify patients with cognitive impairment. This study aimed to examine the diagnostic value of the Montreal Cognitive Assessment (MoCA) in patients after OHCA**.**
Methods: Survivors (age ≥ 18 years) of OHCA completed the MoCA and a gold standard neuropsychological test battery, including tests for memory, attention, perception, language, reasoning, and executive functioning, at around one year after OHCA. Results of the MoCA are related to the results of the neuropsychological test battery. Analyses of diagnostic accuracy included receiver operating characteristics and calculation of predictive values**.**
Results: We included 54 OHCA survivors (mean age = 57.3, 74% male). The area under the curve (AUC) was 0.8, 95% CI [0.67, 0.93]. The MoCA showed excellent sensitivity of 86%, 95% CI [57, 98] and adequate specificity of 70.0%, 95% CI [53, 83] to detect cognitive impairment at the regular cut-off score of 26. The positive predictive value of the MoCA was 50%, 95% CI [30, 70] and the negative predictive value was 93%, 95% CI [76, 99]**.**
Conclusion: This study shows that the MoCA may be a valid cognitive screening instrument for use in the OHCA patient population.

Gepubliceerd: Resuscitation. 2022;172:130-6.
Impact factor: 6.251 ; Q1

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42. Study protocol of the GLOW study: maximising treatment options for recurrent glioblastoma patients by whole genome sequencing-based diagnostics-a prospective multicenter cohort study
van Opijnen MP, Broekman MLD, de Vos FYF, Cuppen E, van der Hoeven JJM, van Linde ME, Compter A, Beerepoot LV, van den Bent MJ, Vos MJ, Fiebrich HB, Koekkoek JAF, Hoeben A, Kho KH, Driessen CML, Jeltema HR, Robe P, Maas SLN.

Background: Glioblastoma (GBM), the most common glial primary brain tumour, is without exception lethal. Every year approximately 600 patients are diagnosed with this heterogeneous disease in The Netherlands. Despite neurosurgery, chemo -and radiation therapy, these tumours inevitably recur. Currently, there is no gold standard at time of recurrence and treatment options are limited. Unfortunately, the results of dedicated trials with new drugs have been very disappointing. The goal of the project is to obtain the evidence for changing standard of care (SOC) procedures to include whole genome sequencing (WGS) and consequently adapt care guidelines for this specific patient group with very poor prognosis by offering optimal and timely benefit from novel therapies, even in the absence of traditional registration trials for this small volume cancer indication**.**
Methods: The GLOW study is a prospective diagnostic cohort study executed through collaboration of the Hartwig Medical Foundation (Hartwig, a non-profit organisation) and twelve Dutch centers that perform neurosurgery and/or treat GBM patients. A total of 200 patients with a first recurrence of a glioblastoma will be included. Dual primary endpoint is the percentage of patients who receive targeted therapy based on the WGS report and overall survival. Secondary endpoints include WGS report success rate and number of targeted treatments available based on WGS reports and number of patients starting a treatment in presence of an actionable variant. At recurrence, study participants will undergo SOC neurosurgical resection. Tumour material will then, together with a blood sample, be sent to Hartwig where it will be analysed by WGS. A diagnostic report with therapy guidance, including potential matching off-label drugs and available clinical trials will then be sent back to the treating physician for discussing of the results in molecular tumour boards and targeted treatment decision making.
Discussion: The GLOW study aims to provide the scientific evidence for changing the SOC diagnostics for patients with a recurrent glioblastoma by investigating complete genome diagnostics to maximize treatment options for this patient group.
Trial registration: ClinicalTrials.gov Identifier: NCT05186064.

Gepubliceerd: BMC Med Genomics. 2022;15(1):233.
Impact factor: 3.622 ; Q2

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43. Study of effect of nimodipine and acetaminophen on postictal symptoms in depressed patients after electroconvulsive therapy (SYNAPSE)
Verdijk J, Pottkämper JCM, Verwijk E, van Wingen GA, van Putten M, Hofmeijer J, van Waarde JA.

Background: Postictal phenomena as delirium, headache, nausea, myalgia, and anterograde and retrograde amnesia are common manifestations after seizures induced by electroconvulsive therapy (ECT). Comparable postictal phenomena also contribute to the burden of patients with epilepsy. The pathophysiology of postictal phenomena is poorly understood and effective treatments are not available. Recently, seizure-induced cyclooxygenase (COX)-mediated postictal vasoconstriction, accompanied by cerebral hypoperfusion and hypoxia, has been identified as a candidate mechanism in experimentally induced seizures in rats. Vasodilatory treatment with acetaminophen or calcium antagonists reduced postictal hypoxia and postictal symptoms. The aim of this clinical trial is to study the effects of acetaminophen and nimodipine on postictal phenomena after ECT-induced seizures in patients suffering major depressive disorder. We hypothesize that (1) acetaminophen and nimodipine will reduce postictal electroencephalographic (EEG) phenomena, (2) acetaminophen and nimodipine will reduce magnetic resonance imaging (MRI) measures of postictal cerebral hypoperfusion, (3) acetaminophen and nimodipine will reduce clinical postictal phenomena, and (4) postictal phenomena will correlate with measures of postictal hypoperfusion**.**
Methods: We propose a prospective, three-condition cross-over design trial with randomized condition allocation, open-label treatment, and blinded end-point evaluation (PROBE design). Thirty-three patients (age > 17 years) suffering from a depressive episode treated with ECT will be included.

Randomly and alternately, single doses of nimodipine (60 mg), acetaminophen (1000 mg), or water will be given two hours prior to each ECT session with a maximum of twelve sessions per patient. The primary outcome measure is 'postictal EEG recovery time', expressed and quantified as an adapted version of the temporal brain symmetry index, yielding a time constant for the duration of the postictal state on EEG. Secondary outcome measures include postictal cerebral perfusion, measured by arterial spin labelling MRI, and the postictal clinical 'time to orientation'.
Discussion: With this clinical trial, we will systematically study postictal EEG, MRI and clinical phenomena after ECT-induced seizures and will test the effects of vasodilatory treatment intending to reduce postictal symptoms. If an effect is established, this will provide a novel treatment of postictal symptoms in ECT patients. Ultimately, these findings may be generalized to patients with epilepsy.
Trial registration: Inclusion in SYNAPSE started in December 2019. Prospective trial registration number is NCT04028596 on the international clinical trial register on July 22, 2019.

Gepubliceerd: Trials. 2022;23(1):324.
Impact factor: 2.728 ; Q4

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44. Clinical Outcome After Endovascular Treatment in Patients With Active Cancer and Ischemic Stroke: A MR CLEAN Registry Substudy
Verschoof MA, Groot AE, de Bruijn S, Roozenbeek B, van der Worp HB, Dippel DWJ, Emmer BJ, Roosendaal SD, Majoie C, Roos Y, Coutinho JM, MR CLEAN Registry Investigators; Brouwers PJAM.

Background and Objectives: To explore clinical and safety outcomes of patients with acute ischemic stroke (AIS) and active cancer after endovascular treatment (EVT)**.**
Methods: Using data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry, we compared patients with active cancer (defined as cancer diagnosed within 12 months before stroke, metastatic disease, or current cancer treatment) to patients without cancer. Outcomes were 90-day modified Rankin Scale (mRS) score, mortality, successful reperfusion (expanded Treatment in Cerebral Infarction score ≥2b), symptomatic intracranial hemorrhage (sICH), and recurrent stroke. Subgroup analyses were performed in patients with a prestroke mRS score of 0 or 1 and according to treatment setting (curative or palliative). Analyses were adjusted for prognostic variables**.**
Results: Of 2,583 patients who underwent EVT, 124 (4.8%) had active cancer. They more often had prestroke disability (mRS score ≥2: 34.1% vs 16.6%). The treatment setting was palliative in 25.3% of the patients. There was a shift toward worse functional outcome at 90 days in patients with active cancer (adjusted common odds ratio [acOR] 2.2, 95% confidence interval [CI] 1.5-3.2). At 90 days, patients with active cancer were less often independent (mRS score 0-2: 22.6% vs 42.0%, adjusted OR [aOR] 0.5, 95% CI 0.3-0.8) and more often dead (52.2% vs 26.5%, aOR 3.2, 95% CI 2.1-4.9). Successful reperfusion (67.8% vs 60.5%, aOR 1.4, 95% CI 1.0-2.1) and sICH rates (6.5% vs 5.9%, aOR 1.1, 95% CI 0.5-2.3) did not differ. Recurrent stroke within 90 days was more common in patients with active cancer (4.0% vs 1.3%, aOR 3.1, 95% CI 1.2-8.1). The sensitivity analysis of patients with a prestroke mRS score of 0 or 1 showed that patients with active cancer still had a worse outcome at 90 days (acOR 1.9, 95% CI 1.2-3.0). Patients with active cancer in a palliative treatment setting regained functional independence less often compared to patients in a curative setting (18.2% vs 32.1%), and mortality was higher (81.8% vs 39.3%).
Discussion: Despite similar technical success, patients with active cancer had significantly worse outcomes after EVT for AIS. Moreover, they had an increased risk of recurrent stroke. Nevertheless, about a quarter of the patients regained functional independence, and the risk of other complications, most notably sICH, was not increased. CLASSIFICATION OF EVIDENCE: This study

provides Class I evidence that patients with active cancer undergoing EVT for AIS have worse functional outcomes at 90 days compared to those without active cancer.

Gepubliceerd: Neurology. 2022;98(10):e993-e1001.
Impact factor: 12.258 ; Q1

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45. Predicting Neurological Outcome From Electroencephalogram Dynamics in Comatose Patients After Cardiac Arrest With Deep Learning
Zheng WL, Amorim E, Jing J, Wu O, Ghassemi M, Lee JW, Sivaraju A, Pang T, Herman ST, Gaspard N, Ruijter BJ, Tjepkema-Cloostermans MC, Hofmeijer J, van Putten M, Westover MB.

Objective: Most cardiac arrest patients who are successfully resuscitated are initially comatose due to hypoxic-ischemic brain injury. Quantitative electroencephalography (EEG) provides valuable prognostic information. However, prior approaches largely rely on snapshots of the EEG, without taking advantage of temporal information**.**
Methods: We present a recurrent deep neural network with the goal of capturing temporal dynamics from longitudinal EEG data to predict long-term neurological outcomes. We utilized a large international dataset of continuous EEG recordings from 1,038 cardiac arrest patients from seven hospitals in Europe and the US. Poor outcome was defined as a Cerebral Performance Category (CPC) score of 3-5, and good outcome as CPC score 0-2 at 3 to 6-months after cardiac arrest. Model performance is evaluated using 5-fold cross validation**.**
Results: The proposed approach provides predictions which improve over time, beginning from an area under the receiver operating characteristic curve (AUC-ROC) of 0.78 (95% CI: 0.72-0.81) at 12 hours, and reaching 0.88 (95% CI: 0.85-0.91) by 66 h after cardiac arrest. At 66 h, (sensitivity, specificity) points of interest on the ROC curve for predicting poor outcomes were (32,99)%, (55,95)%, and (62,90)%, (99,23)%, (95,47)%, and (90,62)%; whereas for predicting good outcome, the corresponding operating points were (17,99)%, (47,95)%, (62,90)%, (99,19)%, (95,48)%, (70,90)%. Moreover, the model provides predicted probabilities that closely match the observed frequencies of good and poor outcomes (calibration error 0.04). CONCLUSIONS AND SIGNIFICANCE: These findings suggest that accounting for EEG trend information can substantially improve prediction of neurologic outcomes for patients with coma following cardiac arrest.

Gepubliceerd: IEEE Trans Biomed Eng. 2022;69(5):1813-25.
Impact factor: 4.756 ; Q2

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46. Effect of first pass reperfusion on outcome in patients with posterior circulation ischemic stroke
den Hartog SJ, Roozenbeek B, Boodt N, Bruggeman AAE, van Es A, Emmer BJ, Majoie C, van den Wijngaard IR, van Doormaal PJ, van Zwam WH, Lingsma HF, Dippel DWJ, MR CLEAN Registry investigators; Brouwers PJAM, Gerrits D.

Background: First pass reperfusion (FPR), that is, excellent reperfusion (expanded treatment in cerebral ischemia (eTICI) 2C-3) in one pass, after endovascular treatment (EVT) of an occluded artery in the anterior circulation, is associated with favorable clinical outcome, even when compared with multiple pass excellent reperfusion (MPR). In patients with posterior circulation ischemic stroke (PCS), the same association is expected, but currently unknown. We aimed to assess characteristics associated with FPR and the influence of FPR versus MPR on outcomes in patients with PCS**.**
Methods: We used data from the MR CLEAN Registry, a prospective observational study. The effect of FPR on 24-hour National Institutes of Health Stroke Scale (NIHSS) score, as percentage reduction,

and on modified Rankin Scale (mRS) scores at 3 months, was tested with linear and ordinal logistic regression models**.**
Results: Of 224 patients with PCS, 45 patients had FPR, 47 had MPR, and 90 had no excellent reperfusion (eTICI <2C). We did not find an association between any of the patient, imaging, or treatment characteristics and FPR. FPR was associated with better NIHSS (-45% (95% CI: -65% to -12%)) and better mRS scores (adjusted common odds ratio (acOR): 2.16 (95% CI: 1.23 to 3.79)) compared with no FPR. Outcomes after FPR were also more favorable compared with MPR, but the effect was smaller and not statistically significant (NIHSS: -14% (95% CI: -51% to 49%), mRS acOR: 1.50 (95% CI: 0.75 to 3.00)).
Conclusions: FPR in patients with PCS is associated with favorable clinical outcome in comparison with no FPR. In comparison with MPR, the effect of FPR was no longer statistically significant. Nevertheless, our data support the notion that FPR should be the treatment target to pursue in every patient treated with EVT.

Gepubliceerd: J Neurointerv Surg. 2022;14(4):333-40.
Impact factor: 8.572 ; Q1

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47. Treating Rhythmic and Periodic EEG Patterns in Comatose Survivors of Cardiac Arrest
Ruijter BJ, Keijzer HM, Tjepkema-Cloostermans MC, Blans MJ, Beishuizen A, Tromp SC, Scholten E, Horn J, van Rootselaar AF, Admiraal MM, van den Bergh WM, Elting JJ, Foudraine NA, Kornips FHM, van Kranen-Mastenbroek V, Rouhl RPW, Thomeer EC, Moudrous W, Nijhuis FAP, Booij SJ, Hoedemaekers CWE, Doorduin J, Taccone FS, van der Palen J, van Putten M, Hofmeijer J, Telstar Investigators.

Background: Whether the treatment of rhythmic and periodic electroencephalographic (EEG) patterns in comatose survivors of cardiac arrest improves outcomes is uncertain.
Methods: We conducted an open-label trial of suppressing rhythmic and periodic EEG patterns detected on continuous EEG monitoring in comatose survivors of cardiac arrest. Patients were randomly assigned in a 1:1 ratio to a stepwise strategy of antiseizure medications to suppress this activity for at least 48 consecutive hours plus standard care (antiseizure-treatment group) or to standard care alone (control group); standard care included targeted temperature management in both groups. The primary outcome was neurologic outcome according to the score on the Cerebral Performance Category (CPC) scale at 3 months, dichotomized as a good outcome (CPC score indicating no, mild, or moderate disability) or a poor outcome (CPC score indicating severe disability, coma, or death). Secondary outcomes were mortality, length of stay in the intensive care unit (ICU), and duration of mechanical ventilation.
Results: We enrolled 172 patients, with 88 assigned to the antiseizure-treatment group and 84 to the control group. Rhythmic or periodic EEG activity was detected a median of 35 hours after cardiac arrest; 98 of 157 patients (62%) with available data had myoclonus. Complete suppression of rhythmic and periodic EEG activity for 48 consecutive hours occurred in 49 of 88 patients (56%) in the antiseizure-treatment group and in 2 of 83 patients (2%) in the control group. At 3 months, 79 of 88 patients (90%) in the antiseizure-treatment group and 77 of 84 patients (92%) in the control group had a poor outcome (difference, 2 percentage points; 95% confidence interval, -7 to 11; P = 0.68). Mortality at 3 months was 80% in the antiseizure-treatment group and 82% in the control group. The mean length of stay in the ICU and mean duration of mechanical ventilation were slightly longer in the antiseizure-treatment group than in the control group.
Conclusions: In comatose survivors of cardiac arrest, the incidence of a poor neurologic outcome at 3 months did not differ significantly between a strategy of suppressing rhythmic and periodic EEG activity with the use of antiseizure medication for at least 48 hours plus standard care and standard care alone.

(Funded by the Dutch Epilepsy Foundation; TELSTAR ClinicalTrials.gov number, NCT02056236.).

Gepubliceerd: N Engl J Med. 2022;386(8):724-34.
Impact factor: 176.082 ; Q1

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48. Child Neurology: Maternal Transmission of Congenital Myotonic Dystrophy Type 2: Case Report
Tieleman AA, Damen MJ, Verrips A, Roelofs M, Kamsteeg EJ, Voermans NC.

Gepubliceerd: Neurology. 2022.
Impact factor: 12.258; Q1

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49. Estimation of treatment effects in observational stroke care data: comparison of statistical approaches
Amini M, van Leeuwen N, Eijkenaar F, van de Graaf R, Samuels N, van Oostenbrugge R, van den Wijngaard IR, van Doormaal PJ, Roos Y, Majoie C, Roozenbeek B, Dippel D, Burke J, Lingsma HF, MR Clean Registry Investigators: Brouwers PJAM

Introduction: Various statistical approaches can be used to deal with unmeasured confounding when estimating treatment effects in observational studies, each with its own pros and cons. This study aimed to compare treatment effects as estimated by different statistical approaches for two interventions in observational stroke care data.
Patients and methods: We used prospectively collected data from the MR CLEAN registry including all patients (n = 3279) with ischemic stroke who underwent endovascular treatment (EVT) from 2014 to 2017 in 17 Dutch hospitals. Treatment effects of two interventions - i.e., receiving an intravenous thrombolytic (IVT) and undergoing general anesthesia (GA) before EVT - on good functional outcome (modified Rankin Scale </=2) were estimated. We used three statistical regression-based approaches that vary in assumptions regarding the source of unmeasured confounding: individual-level (two subtypes), ecological, and instrumental variable analyses. In the latter, the preference for using the interventions in each hospital was used as an instrument.
Results: Use of IVT (range 66-87%) and GA (range 0-93%) varied substantially between hospitals. For IVT, the individual-level (OR ~ 1.33) resulted in significant positive effect estimates whereas in instrumental variable analysis no significant treatment effect was found (OR 1.11; 95% CI 0.58-1.56). The ecological analysis indicated no statistically significant different likelihood (beta = - 0.002%; P = 0.99) of good functional outcome at hospitals using IVT 1% more frequently. For GA, we found non-significant opposite directions of points estimates the treatment effect in the individual-level (ORs ~ 0.60) versus the instrumental variable approach (OR = 1.04). The ecological analysis also resulted in a non-significant negative association (0.03% lower probability).
Discussion and conclusion: Both magnitude and direction of the estimated treatment effects for both interventions depend strongly on the statistical approach and thus on the source of (unmeasured) confounding. These issues should be understood concerning the specific characteristics of data, before applying an approach and interpreting the results. Instrumental variable analysis might be considered when unobserved confounding and practice variation is expected in observational multicenter studies.

Gepubliceerd: BMC Med Res Methodol. 2022;22(1):103.
Impact factor: 4.000; Q1

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50. Association of Ischemic Core Imaging Biomarkers With Post-Thrombectomy Clinical Outcomes in the MR CLEAN Registry
Koopman MS, Hoving JW, Kappelhof M, Berkhemer OA, Beenen LFM, van Zwam WH, de Jong H, Dankbaar JW, Dippel DWJ, Coutinho JM, Marquering HA, Emmer BJ, Majoie C, Mr Clean Registry Investigators: Brouwers PJAM.

Background: A considerable proportion of acute ischemic stroke patients treated with endovascular thrombectomy (EVT) are dead or severely disabled at 3 months despite successful reperfusion. Ischemic core imaging biomarkers may help to identify patients who are more likely to have a poor outcome after endovascular thrombectomy (EVT) despite successful reperfusion. We studied the association of CT perfusion-(CTP), CT angiography-(CTA), and non-contrast CT-(NCCT) based imaging markers with poor outcome in patients who underwent EVT in daily clinical practice.
Methods: We included EVT-treated patients (July 2016-November 2017) with an anterior circulation occlusion from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry with available baseline CTP, CTA, and NCCT. We used multivariable binary and ordinal logistic regression to analyze the association of CTP ischemic core volume, CTA-Collateral Score (CTA-CS), and Alberta Stroke Program Early CT Score (ASPECTS) with poor outcome (modified Rankin Scale score (mRS) 5-6) and likelihood of having a lower score on the mRS at 90 days.
Results: In 201 patients, median core volume was 13 (IQR 5-41) mL. Median ASPECTS was 9 (IQR 8-10). Most patients had grade 2 (83/201; 42%) or grade 3 (28/201; 14%) collaterals. CTP ischemic core volume was associated with poor outcome [aOR per 10 mL 1.02 (95%CI 1.01-1.04)] and lower likelihood of having a lower score on the mRS at 90 days [aOR per 10 mL 0.85 (95% CI 0.78-0.93)]. In multivariable analysis, neither CTA-CS nor ASPECTS were significantly associated with poor outcome or the likelihood of having a lower mRS.
Conclusion: In our population of patients treated with EVT in daily clinical practice, CTP ischemic core volume is associated with poor outcome and lower likelihood of shift toward better outcome in contrast to either CTA-CS or ASPECTS.

Gepubliceerd: Front Neurol. 2021;12:771367.
Impact factor 3.400; Q2

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51. Comparative effectiveness and safety of non-vitamin K antagonists for atrial fibrillation in clinical practice: GLORIA-AF Registry
Lip GYH, Kotalczyk A, Teutsch C, Diener HC, Dubner SJ, Halperin JL, Ma CS, Rothman KJ, Marler S, Gurusamy VK, Huisman MV, Gloria-Af Investigators: Brouwers PJAM.

Background and purpose: Prospectively collected data comparing the safety and effectiveness of individual non-vitamin K antagonists (NOACs) are lacking. Our objective was to directly compare the effectiveness and safety of NOACs in patients with newly diagnosed atrial fibrillation (AF).
Methods: In GLORIA-AF, a large, prospective, global registry program, consecutive patients with newly diagnosed AF were followed for 3 years. The comparative analyses for (1) dabigatran vs rivaroxaban or apixaban and (2) rivaroxaban vs apixaban were performed on propensity score (PS)-matched patient sets. Proportional hazards regression was used to estimate hazard ratios (HRs) for outcomes of interest.
Results: The GLORIA-AF Phase III registry enrolled 21,300 patients between January 2014 and December 2016. Of these, 3839 were prescribed dabigatran, 4015 rivaroxaban and 4505 apixaban, with median ages of 71.0, 71.0, and 73.0 years, respectively. In the PS-matched set, the adjusted HRs and 95% confidence intervals (CIs) for dabigatran vs rivaroxaban were, for stroke: 1.27 (0.79-2.03), major bleeding 0.59 (0.40-0.88), myocardial infarction 0.68 (0.40-1.16), and all-cause death 0.86

(0.67-1.10). For the comparison of dabigatran vs apixaban, in the PS-matched set, the adjusted HRs were, for stroke 1.16 (0.76-1.78), myocardial infarction 0.84 (0.48-1.46), major bleeding 0.98 (0.63-1.52) and all-cause death 1.01 (0.79-1.29). For the comparison of rivaroxaban vs apixaban, in the PS-matched set, the adjusted HRs were, for stroke 0.78 (0.52-1.19), myocardial infarction 0.96 (0.63-1.45), major bleeding 1.54 (1.14-2.08), and all-cause death 0.97 (0.80-1.19).
Conclusions: Patients treated with dabigatran had a 41% lower risk of major bleeding compared with rivaroxaban, but similar risks of stroke, MI, and death. Relative to apixaban, patients treated with dabigatran had similar risks of stroke, major bleeding, MI, and death. Rivaroxaban relative to apixaban had increased risk for major bleeding, but similar risks for stroke, MI, and death.
Registration: URL: https://www. CLINICALTRIALS: gov . Unique identifiers: NCT01468701, NCT01671007. Date of registration: September 2013.

Gepubliceerd: Clin Res Cardiol. 2022;111(5):560-73.
Impact factor 5.000; Q1

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52. Stroke genetics informs drug discovery and risk prediction across ancestries
Mishra A, Malik R, Hachiya T, Jurgenson T, Namba S, Posner DC, Kamanu FK, Koido M, Le Grand Q, Shi M, He Y, Georgakis MK, Caro I, Krebs K, Liaw YC, Vaura FC, Lin K, Winsvold BS, Srinivasasainagendra V, Parodi L, Bae HJ, Chauhan G, Chong MR, Tomppo L, Akinyemi R, Roshchupkin GV, Habib N, Jee YH, Thomassen JQ, Abedi V, Carcel-Marquez J, Nygaard M, Leonard HL, Yang C, Yonova-Doing E, Knol MJ, Lewis AJ, Judy RL, Ago T, Amouyel P, Armstrong ND, Bakker MK, Bartz TM, Bennett DA, Bis JC, Bordes C, Borte S, Cain A, Ridker PM, Cho K, Chen Z, Cruchaga C, Cole JW, de Jager PL, de Cid R, Endres M, Ferreira LE, Geerlings MI, Gasca NC, Gudnason V, Hata J, He J, Heath AK, Ho YL, Havulinna AS, Hopewell JC, Hyacinth HI, Inouye M, Jacob MA, Jeon CE, Jern C, Kamouchi M, Keene KL, Kitazono T, Kittner SJ, Konuma T, Kumar A, Lacaze P, Launer LJ, Lee KJ, Lepik K, Li J, Li L, Manichaikul A, Markus HS, Marston NA, Meitinger T, Mitchell BD, Montellano FA, Morisaki T, Mosley TH, Nalls MA, Nordestgaard BG, O'Donnell MJ, Okada Y, Onland-Moret NC, Ovbiagele B, Peters A, Psaty BM, Rich SS, Rosand J, Sabatine MS, Sacco RL, Saleheen D, Sandset EC, Salomaa V, Sargurupremraj M, Sasaki M, Satizabal CL, Schmidt CO, Shimizu A, Smith NL, Sloane KL, Sutoh Y, Sun YV, Tanno K, Tiedt S, Tatlisumak T, Torres-Aguila NP, Tiwari HK, Tregouet DA, Trompet S, Tuladhar AM, Tybjaerg-Hansen A, van Vugt M, Vibo R, Verma SS, Wiggins KL, Wennberg P, Woo D, Wilson PWF, Xu H, Yang Q, Yoon K, Consortium C, Consortium I, Dutch Parelsnoer Initiative Cerebrovascular Disease Study G, Estonian B, Consortium PQ, FinnGen C, Network NSG, Consortium M, Consortium S, China Kadoorie Biobank Collaborative G, Program VAMV, International Stroke Genetics C, Biobank J, Consortium C, Consortium G, Millwood IY, Gieger C, Ninomiya T, Grabe HJ, Jukema JW, Rissanen IL, Strbian D, Kim YJ, Chen PH, Mayerhofer E, Howson JMM, Irvin MR, Adams H, Wassertheil-Smoller S, Christensen K, Ikram MA, Rundek T, Worrall BB, Lathrop GM, Riaz M, Simonsick EM, Korv J, Franca PHC, Zand R, Prasad K, Frikke-Schmidt R, de Leeuw FE, Liman T, Haeusler KG, Ruigrok YM, Heuschmann PU, Longstreth WT, Jung KJ, Bastarache L, Pare G, Damrauer SM, Chasman DI, Rotter JI, Anderson CD, Zwart JA, Niiranen TJ, Fornage M, Liaw YP, Seshadri S, Fernandez-Cadenas I, Walters RG, Ruff CT, Owolabi MO, Huffman JE, Milani L, Kamatani Y, Dichgans M, Debette S, Consortium includes Brouwers PJAM.

Previous genome-wide association studies (GWASs) of stroke - the second leading cause of death worldwide - were conducted predominantly in populations of European ancestry(1,2). Here, in cross-ancestry GWAS meta-analyses of 110,182 patients who have had a stroke (five ancestries, 33% non-European) and 1,503,898 control individuals, we identify association signals for stroke and its subtypes at 89 (61 new) independent loci: 60 in primary inverse-variance-weighted analyses and 29 in secondary meta-regression and multitrait analyses. On the basis of internal cross-ancestry validation and an independent follow-up in 89,084 additional cases of stroke (30% non-European)

and 1,013,843 control individuals, 87% of the primary stroke risk loci and 60% of the secondary stroke risk loci were replicated ($P < 0.05$). Effect sizes were highly correlated across ancestries. Cross-ancestry fine-mapping, in silico mutagenesis analysis(3), and transcriptome-wide and proteome-wide association analyses revealed putative causal genes (such as SH3PXD2A and FURIN) and variants (such as at GRK5 and NOS3). Using a three-pronged approach(4), we provide genetic evidence for putative drug effects, highlighting F11, KLKB1, PROC, GP1BA, LAMC2 and VCAM1 as possible targets, with drugs already under investigation for stroke for F11 and PROC. A polygenic score integrating cross-ancestry and ancestry-specific stroke GWASs with vascular-risk factor GWASs (integrative polygenic scores) strongly predicted ischaemic stroke in populations of European, East Asian and African ancestry(5). Stroke genetic risk scores were predictive of ischaemic stroke independent of clinical risk factors in 52,600 clinical-trial participants with cardiometabolic disease. Our results provide insights to inform biology, reveal potential drug targets and derive genetic risk prediction tools across ancestries.

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Impact factor: 64.800; Q1

Totale impact factor: 713.444
Gemiddelde impact factor: 13.720

Aantal artikelen 1e, 2e of laatste auteur: 15
Totale impact factor: 75.430
Gemiddelde impact factor: 5.030

Orthopedie

1. Treatment of decentered developmental dysplasia of the hip under the age of 1 year: an evidence-based clinical practice guideline - Part 2
de Witte PB, van Bergen CJA, de Geest BL, Willeboordse F, van Linge JH, den Hartog YM, Margret MHPF-vDM, Pereboom RM, Robben SGF, Burger BJ, Witlox MA, Witbreuk M.

Background and Purpose: Diagnostics and treatment of developmental dysplasia of the hip (DDH) are highly variable in clinical practice. To obtain more uniform and evidence-based treatment pathways, we developed the 'Dutch guideline for DDH in children < 1 year'. This study describes recommendations for unstable and decentered hips.
Material and Methods: The Appraisal of Guidelines for Research and Evaluation criteria (AGREE II) were applied. A systematic literature review was performed for six predefined guideline questions. Recommendations were developed, based on literature findings, as well as harms/benefits, patient/parent preferences, and costs (GRADE)**.**
Results: The systematic literature search resulted in 843 articles and 11 were included. Final guideline recommendations are (i) Pavlik harness is the preferred first step in the treatment of (sub) luxated hips; (ii) follow-up with ultrasound at 3-4 and 6-8 weeks; (iii) if no centered and stable hip after 6-8 weeks is present, closed reduction is indicated; (iv) if reduction is restricted by limited hip abduction, adductor tenotomy is indicated; (v) in case of open reduction, the anterior, anterolateral, or medial approach is advised, with the choice based on surgical preference and experience; (vi) after reduction (closed/open), a spica cast is advised for 12 weeks, followed by an abduction device in case of residual dysplasia.
Interpretation: This study presents recommendations on the treatment of decentered DDH, based on the available literature and expert consensus, as Part 2 of the first official and national evidence-based 'Guideline for DDH in children < 1 year'. Part 1 describes the guideline sections on centered DDH in a separate article.

Gepubliceerd: EFORT Open Rev. 2022;7(8):542-53.
Impact factor: 4.775 ; Q1

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2. Consensus Statement for Shoulder Impingement: To Operate or Not? Who to Ask for the Consensus Panel
Dorrestijn O, Diercks RL, Lambers Heerspink FO, Veen EJD.

Gepubliceerd: Arthroscopy. 2022;38(5):1385-7.
Impact factor: 1.131 ; Q1

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3. Stigma Toward Bariatric Surgery in the Netherlands, France, and the United Kingdom: Protocol for a Cross-cultural Mixed Methods Study
Garcia FK, Verkooijen KT, Veen EJ, Mulder BC, Koelen MA, Hazebroek EJ.

Background: Bariatric surgery is an effective procedure for the treatment of obesity. Despite this, only 0.1% to 2% of eligible individuals undergo surgery worldwide. The stigma surrounding surgery might be a reason for this. Thus far, no research has systematically studied the nature and implications of bariatric surgery stigma. The limited studies on bariatric surgery stigma are often conducted from the perspective of the public or health care professions and either use small and nonrepresentative samples or fail to capture the full essence and implications of the stigma altogether, including attitudes toward patients and perpetrators of the stigma. In addition, studies

from patients' perspectives are limited and tend to address bariatric surgery stigma superficially or implicitly. Finally, the extent to which cultural factors shape and facilitate this stigma and the experiences of patients have not yet been researched.
Objective: This study aimed to explore the perceptions, experiences, and consequences of bariatric surgery stigma from the perspective of the public, health care professionals, and patients before and after bariatric surgery. Furthermore, although the concept of stigma is universal, every society has specific cultural norms and values that define acceptable attributes and behaviors for its members. Therefore, this study also aimed to explore the extent to which cultural factors influence bariatric surgery stigma by comparing the Netherlands, France, and the United Kingdom**.**
Methods: This paper describes the protocol for a multiphase mixed methods research design. In the first part, we will conduct a scoping review to determine the current knowledge on bariatric surgery stigma and identify knowledge gaps. In the second part, semistructured interviews among patients before and after bariatric surgery will be conducted to explore their experiences and consequences of bariatric surgery stigma. In the third part, surveys will be conducted among both the public and health care professionals to determine the prevalence, nature, and impact of bariatric surgery stigma. Surveys and interviews will be conducted in the Netherlands, France, and the United Kingdom. Finally, data integration will be conducted at the interpretation and reporting levels**.**
Results: The study began in September 2020 and will continue through September 2025. With the results of the review, we will create an overview of the current knowledge regarding bariatric surgery stigma from patients' perspectives. Qualitative data will provide insights into patients' experiences with bariatric surgery stigma. Quantitative data will provide information related to the prevalence and nature of bariatric surgery stigma from the perspective of the public and health care professionals. Both qualitative and quantitative data will be compared for each country.
Conclusions: The findings from this study will lead to new insights that can be used to develop strategies to reduce bariatric surgery stigma and improve access, use, and outcomes of bariatric surgery. INTERNATIONAL REGISTERED REPORT IDENTIFIER (IRRID): PRR1-10.2196/36753.

Gepubliceerd: JMIR Res Protoc. 2022;11(4):e36753.
Impact factor: 0 ; Q NVT

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4. Double-center observational study of minimally invasive sacroiliac joint fusion for sacroiliac joint dysfunction: one-year results
Hermans SMM, Knoef RJH, Schuermans VNE, Schotanus MGM, Nellensteijn JM, van Santbrink H, Curfs I, van Hemert WLW.

Background: For a substantial part of patients with chronic low back pain, the origin is located in the sacroiliac joint (SIJ). Minimally invasive sacroiliac joint fusion (MISJF) is increasingly being implemented as a treatment option in SIJ dysfunction. Despite remaining controversy, evidence continues to increase. This study evaluates the clinical results and safety of MISJF in a double-center consecutive case series in patients with SIJ dysfunction over a one-year observation period**.**
Methods: SIJ complaints were diagnosed after history taking, physical examination and least a 50% reduction of SIJ pain 30-60 min following image-guided injection. Primary outcome measures were patient reported outcome measurements (PROMs), consisting of Visual Analogue Scale (VAS) pain score and EuroQol 5-dimensions 3-levels (EQ-5D-3L). Patients' perspectives on the effects of surgery were collected through questionnaires. Secondary outcome measures were implant positioning and (serious) adverse events ((S)AE's)**.**
Results: A total of 29 patients were included. In 44.8% of patients, SIJ dysfunction was of postpartum origin. The mean VAS-pain score improved from 7.83 (± 1.71) to 4.97 (± 2.63) postoperatively ($p < 0.001$). EQ-5D-3L score improved from 0.266 (± 0.129) to 0.499 (± 0.260) postoperatively

($p < 0.001$). Opioid consumption decreased from 44.8 to 24.1% postoperatively ($p = 0.026$). In 13.7% of patients, an (S)AE occurred**.**
Conclusion: MISJF appears to be an effective and safe procedure in this cohort. Statistically significant and clinically relevant improvements in pain and quality of life were observed one-year postoperatively. Future studies should focus on the long-term outcomes to further evaluate the safety and effectiveness of MISJF.

Gepubliceerd: J Orthop Surg Res. 2022;17(1):570.
Impact factor: 2.677 ; Q2

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5. Accuracy, inter- and intrarater reliability, and user-experience of high tibial osteotomy angle measurements for preoperative planning: manual planning PACS versus semi-automatic software programs
Laven I, Schröder FF, de Graaff F, Rompen JC, Hoogeslag RAG, van Houten AH.

Purpose: To compare the accuracy, inter- and intrarater reliability, and user-experience of manual and semi-automatic preoperative leg-alignment measurement planning software for high tibial osteotomy (HTO)**.**
Methods: Thirty patients (31 lower limbs) who underwent a medial opening wedge HTO between 2017 and 2019 were retrospectively included. The mechanical lateral distal femur angle (mLDFA), mechanical medial proximal tibial angle (mMPTA), and planned correction angle were measured on preoperative long-leg full weight-bearing radiographs utilising PACS Jivex Review® v5.2 manual and TraumaCad® v2.4 semi-automatic planning software. Independent measurements were performed by four raters. Two raters repeated the measurements. Accuracy in the standard error of measurement (SEM), inter- and intrarater reliability, and user-experience were analysed. Additionally, measurements errors of more than 3° were remeasured and reanalysed**.**
Results: The SEMs of all measured varus malalignment angles and planned correction angle were within 0.8° of accuracy for both software programs. Measurements utilising the manual software demonstrated moderate interrater intraclass correlation coefficient (ICC)-values for the mLDFA and mMPTA, and an excellent interrater ICC-value for the correction angle (0.810, 0.779, and 0.981, respectively). Measurements utilising the semi-automatic software indicated excellent interrater ICC-values for the mLDFA, mMPTA, and correction angle (0.980, 0.909, and 0.989, respectively). The intrarater reliability varied substantially per angle, presenting excellent intrarater agreements by both raters (ICC > 0.900) for the correction angle in each software program as well as poor-to-excellent ICC-values for the mLDFA (0.282-0.951 and 0.316-0.926) and mMPTA (0.893-0.934 and 0.594-0.941) in both the manual planning and semi-automatic software. Regarding user-experience, semi-automatic software was preferred by two raters, while the other two raters had no distinctive preference. After remeasurement of five outliers, excellent interrater ICC-values were found for the mLDFA (0.913) and mMPTA (0.957).
Conclusions: Semi-automatic software outperforms the manual software when user-experience and outliers are considered. However, both software programs provide similar performance after remeasurement of the human-related erroneous outliers. For clinical practice, both programs can be utilised for HTO planning. LEVEL OF EVIDENCE: Diagnostic study, Level III.

Gepubliceerd: J Exp Orthop. 2022;9(1):44.
Impact factor: 0 ; Q NVT

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6. Acute haematogenous periprosthetic joint infection due to Streptococcus sanguinis along with coexistent crystalline arthropathy after total knee arthroplasty: a rare combination

Malkus JB, Goedhart LM, Verra WC.

A man in his 60s, with a medical history of gout, underwent total knee arthroplasty of his right knee followed by expeditious rehabilitation. Seven months after surgery, he was referred to the emergency ward with sudden onset of pain and swelling of his right knee accompanied with fever. Further inquiry revealed no trauma, infection or skin lesions besides a tongue bite several weeks earlier. An impaired range motion of the knee was seen on physical examination along with a tachycardia. Laboratory studies showed a C reactive protein of 345 mg/L, after which a debridement, antibiotics and implant retention procedure was performed. Intraoperatively obtained synovial fluid showed monosodium urate crystals consistent with crystalline arthropathy (ie, gout). However, unexpectedly, Streptococcus sanguinis was identified in all microbiological cultures too, confirming a coexistent periprosthetic joint infection. After comprehensive antibiotic treatment and gout flare therapy, this patient made a full recovery with retention of the implant.

Gepubliceerd: BMJ Case Rep. 2022;15(5).
Impact factor: 0.170; Q3

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7. Multicomponent Prehabilitation as a Novel Strategy for Preventing Delirium in Older Chronic Limb Threatening Ischemia Patients: A Study Protocol
Meulenbroek AL, Faes MC, van Mil SR, Buimer MG, de Groot HGW, Veen EJ, Ho GH, Boonman-de Winter LJM, de Vries J, van Gorkom R, Toonders F, van Alphen R, van Overveld K, Verbogt N, Steyerberg EW, van der Laan L.

Objective: Chronic limb threatening ischemia is the final stage of peripheral arterial disease. Current treatment is based on revascularization to preserve the leg. In the older, hospitalized chronic limb threatening ischemia patient, delirium is a frequent and severe complication after revascularization. Delirium leads to an increased length of hospital stay, a higher mortality rate and a decrease in quality of life. Currently, no specific guidelines to prevent delirium in chronic limb threatening ischemia patients exist. We aim to evaluate the effect of a multicomponent, multidisciplinary prehabilitation program on the incidence of delirium in chronic limb threatening ischemia patients ≥65 years.
Design:A prospective observational cohort study to investigate the effects of the program on the incidence of delirium will be performed in a large teaching hospital in the Netherlands. This manuscript describes the design of the study and the content of this specific prehabilitation program**.**
Methods: Chronic limb threatening ischemia patients ≥65 years that require revascularization will participate in the program. This program focuses on optimizing the patient's overall health and includes delirium risk assessment, nutritional optimization, home-based physical therapy, iron infusion in case of anaemia and a comprehensive geriatric assessment in case of frailty. The primary outcome is the incidence of delirium. Secondary outcomes include quality of life, amputation-free survival, length of hospital stay and mortality. Exclusion criteria are the requirement of acute treatment or patients who are mentally incompetent to understand the procedures of the study or to complete questionnaires. A historical cohort from the same hospital is used as a control group.
Discussion: This study will clarify the effect of a prehabilitation program on delirium incidence in chronic limb threatening ischemia patients. New insights will be obtained on optimizing a patient's preoperative mental and physical condition to prevent postoperative complications, including delirium. TRIAL: This protocol is registered at the Netherlands National Trial Register (NTR) number: NL9380.

Gepubliceerd: Clin Interv Aging. 2022;17:767-76.

Impact factor: 3.829; Q3

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8. Developing an Intervention and Evaluation Model of Outdoor Therapy for Employee Burnout: Unraveling the Interplay Between Context, Processes, and Outcomes
Pijpker R, Veen EJ, Vaandrager L, Koelen M, Bauer GF.

Background: Burnout is a major societal issue adversely affecting employees' health and performance, which over time results in high sick leave costs for organizations. Traditional rehabilitation therapies show suboptimal effects on reducing burnout and the return-to-work process. Based on the health-promoting effects of nature, taking clients outdoors into nature is increasingly being used as a complementary approach to traditional therapies, and evidence of their effectiveness is growing. Theories explaining how the combination of general psychological support and outdoor-specific elements can trigger the rehabilitation process in outdoor therapy are often lacking, however, impeding its systematic research.
Aim: The study aims to develop an intervention and evaluation model for outdoor therapy to understand and empirically evaluate whether and how such an outdoor intervention may work for rehabilitation after burnout.
Methodological approach: We build on the exemplary case of an outdoor intervention for rehabilitation after burnout, developed by outdoor clinical psychologists in Netherlands. We combined the generic context, process, and outcome evaluation model and the burnout recovery model as an overarching deductive frame. We then inductively specified the intervention and evaluation model of outdoor therapy, building on the following qualitative data: semi-structured interviews with outdoor clinical psychologists and former clients; a content analysis of the intervention protocol; and reflective meetings with the intervention developers and health promotion experts**.**
Results: We identified six key outdoor intervention elements: (1) physical activity; (2) reconnecting body and mind; (3) nature metaphors; (4) creating relationships; (5) observing natural interactions; and (6) experiential learning. The results further showed that the implementation of these elements may facilitate the rehabilitation process after burnout in which proximal, intermediate, and distal outcomes emerge. Finally, the results suggested that this implementation process depends on the context of the therapist (e.g., number of clients per day), therapy (e.g., privacy issues), and of the clients (e.g., affinity to nature)**.**
Conclusion: The intervention and evaluation model for outdoor therapy shows how key outdoor intervention elements may contribute to the rehabilitation process after burnout. However, our model needs to be further tested among a larger group of clients to empirically evaluate whether and how outdoor therapy can support rehabilitation.

Gepubliceerd: Front Psychol. 2022;13:785697.
Impact factor: 4.232 ; Q1

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9. A tailored intervention does not reduce low value MRI's and arthroscopies in degenerative knee disease when the secular time trend is taken into account: a difference-in-difference analysis
Rietbergen T, Marang-van de Mheen PJ, de Graaf J, Diercks RL, Janssen RPA, van der Linden-van der Zwaag HMJ, van den Akker-van Marle ME, Steyerberg EW, Nelissen R, van Bodegom-Vos L, SMART study group; Zeegers AVCM.

Purpose: To evaluate the effectiveness of a tailored intervention to reduce low value MRIs and arthroscopies among patients ≥ 50 years with degenerative knee disease in 13 Dutch orthopaedic centers (intervention group) compared with all other Dutch orthopaedic centers (control group)**.**

Methods: All patients with degenerative knee disease ≥ 50 years admitted to Dutch orthopaedic centers from January 2016 to December 2018 were included. The tailored intervention included participation of clinical champions, education on the Dutch Choosing Wisely recommendation for MRI's and arthroscopies in degenerative knee disease, training of orthopaedic surgeons to manage patient expectations, performance feedback, and provision of a patient brochure. A difference-in-difference analysis was used to compare the time trend before (admitted January 2016-June 2017) and after introduction of the intervention (July 2017-December 2018) between intervention and control hospitals. Primary outcome was the monthly percentage of patients receiving a MRI or knee arthroscopy, weighted by type of hospital**.**
Results: 136,446 patients were included, of whom 32,163 were treated in the intervention hospitals. The weighted percentage of patients receiving a MRI on average declined by 0.15% per month (β = -0.15, P < 0.001) and by 0.19% per month for arthroscopy (β = -0.19, P < 0.001). However, these changes over time did not differ between intervention and control hospitals, neither for MRI (β = -0.74, P = 0.228) nor arthroscopy (β = 0.13, P = 0.688).
Conclusions: The extent to which patients ≥ 50 years with degenerative knee disease received a MRI or arthroscopy declined significantly over time, but could not be attributed to the tailored intervention. This secular downward time trend may reflect anoverall focus of reducing low value care in The Netherlands. LEVEL OF EVIDENCE: III.

Gepubliceerd: Knee Surg Sports Traumatol Arthrosc. 2022;30(12):4134-43.
Impact factor: 4.114 ; Q1

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10. Performing a knee arthroscopy among patients with degenerative knee disease: one-third is potentially low value care

Rietbergen T, Marang-van de Mheen PJ, Diercks RL, Janssen RPA, van der Linden-van der Zwaag HMJ, Nelissen R, Steyerberg EW, van Bodegom-Vos L, SMART study group; Zeegers AVCM.

Purpose: The purpose of this study was to assess in which proportion of patients with degenerative knee disease aged 50+ in whom a knee arthroscopy is performed, no valid surgical indication is reported in medical records, and to explore possible explanatory factors**.**
Methods: A retrospective study was conducted using administrative data from January to December 2016 in 13 orthopedic centers in the Netherlands. Medical records were selected from a random sample of 538 patients aged 50+ with degenerative knee disease in whom arthroscopy was performed, and reviewed on reported indications for the performed knee arthroscopy. Valid surgical indications were predefined based on clinical national guidelines and expert opinion (e.g., truly locked knee). A knee arthroscopy without a reported valid indication was considered potentially low value care. Multivariate logistic regression analysis was performed to assess whether age, diagnosis ("Arthrosis" versus "Meniscal lesion"), and type of care trajectory (initial or follow-up) were associated with performing a potentially low value knee arthroscopy**.**
Results: Of 26,991 patients with degenerative knee disease, 2556 (9.5%) underwent an arthroscopy in one of the participating orthopedic centers. Of 538 patients in whom an arthroscopy was performed, 65.1% had a valid indication reported in the medical record and 34.9% without a reported valid indication. From the patients without a valid indication, a joint patient-provider decision or patient request was reported as the main reason. Neither age [OR 1.013 (95% CI 0.984-1.043)], diagnosis [OR 0.998 (95% CI 0.886-1.124)] or type of care trajectory [OR 0.989 (95% CI 0.948-1.032)] were significantly associated with performing a potentially low value knee arthroscopy.
Conclusions: In a random sample of knee arthroscopies performed in 13 orthopedic centers in 2016, 65% had valid indications reported in the medical records but 35% were performed without a reported valid indication and, therefore, potentially low value care. Patient and/or surgeons preference may play a large role in the decision to perform an arthroscopy without a valid indication.

Therefore, interventions should be developed to increase adherence to clinical guidelines by surgeons that target invalid indications for a knee arthroscopy to improve care. LEVEL OF EVIDENCE: IV.

Gepubliceerd: Knee Surg Sports Traumatol Arthrosc. 2022;30(5):1568-74.
Impact factor: 4.114 ; Q1

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11. Agreement on fixation of pediatric supracondylar humerus fractures
Spierenburg W, Dekker ABE, Doornberg JN, Krijnen P, van den Bekerom MPJ, Schipper IB.

Background: Pediatric supracondylar humerus fractures (pSCHFs) may be challenging injuries to treat because of the potential residual deformity. There is debate regarding the technical aspects of adequate closed reduction and crossed Kirschner wire (K-wire) fixation.
Purpose: Do surgeons have an agreement on the aspects of the fixation of pSCHFs?
Methods: Radiographs of 20 patients from a cohort of 154 patients with pSCHFs treated with closed reduction and crossed K-wire fixation were selected. Forty-four surgeons viewed the postoperative radiographs and diagnosed the presence or absence of technical flaws and made a recommendation for or against reoperation. An expert panel of three orthopedic and trauma surgeons provided a reference standard for technical factors. Furthermore, final outcome 2 years after trauma was assessed**.**
Results: There was limited agreement on potential technical flaws (ICC 0.15-0.28), radiographic measures of alignment (ICC for anterior humeral line and Baumann angle of 0.37 and 0.23 respectively), the quality of postoperative reduction, position of the elbow in cast, and recommendation for repeat surgery (ICCs between 0.23 and 0.40). Sensitivity and specificity for these questions ranged from 0.59 to 0.90. There was no correlation between the voted quality of postoperative reduction and loss of reduction or final function.
Conclusions: Surgeons have limited agreement on the quality of postoperative results in pSCHFs and the indication for reoperation. Reviewing postoperative radiographs may present a good learning opportunity and could help improve skills, but it is not a validated method for quality control and has to be seen in light of clinical outcome.

Gepubliceerd: Eur J Trauma Emerg Surg. 2022;48(5):4277-82.
Impact factor: 2.374 ; Q3

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12. Willingness to participate in a hypothetical orthopaedic diagnostic and invasive surgical trial
Spierenburg W, van Wier MF, Poolman RW.

Objective: To investigate patient preferences and the determinants of participation willingness in orthopaedic diagnostic or invasive surgical randomized controlled trials**.**
Methods: This observational study included one hundred patients visiting an orthopaedic clinic. The patients answered if they were willing to participate in a hypothetical invasive and diagnostic trial among patients with a distal radius fracture**.**
Results: We found no difference in participation willingness in either the invasive surgical (66/100) or the diagnostic trial (68/100, p = 0.76). Willingness to participate was not associated with age, gender, country of origin, level of education, marital status, or distance of home from the hospital with the confidence interval for all odds ratios including the value 1. Patients who expressed willingness to participate do so because they wanted to contribute to science; patients who declined to participate wanted to speak with a doctor and to be better informed**.**

Conclusion: This study showed a high rate of willingness to participate in orthopaedic surgical invasive trials and in diagnostic trials. Nevertheless, to ensure participation, it is recommended to put emphasis on the contribution to science and to give adequate information about the trial including the opportunity to talk to a doctor.

Gepubliceerd: Injury. 2022;53(6):1966-71.
Impact factor: 2.687 ; Q2

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13. Treatment of centered developmental dysplasia of the hip under the age of 1 year: an evidence-based clinical practice guideline - Part 1
van Bergen CJA, de Witte PB, Willeboordse F, de Geest BL, Foreman-van Drongelen M, Burger BJ, den Hartog YM, van Linge JH, Pereboom RM, Robben SGF, Witlox MA, Witbreuk M.

Despite the high incidence of developmental dysplasia of the hip (DDH), treatment is very diverse. Therefore, the Dutch Orthopedic Society developed a clinical practice guideline with recommendations for optimal and uniform treatment of DDH. This article summarizes the guideline on centered DDH (i.e. Graf types 2A-C). The guideline development followed the criteria of Appraisal of Guidelines for Research and Evaluation II. A systematic literature review was performed to identify randomized controlled trials and comparative cohort studies including children <1 year with centered DDH. Articles were included that compared (1) treatment with observation, (2) different abduction devices, (3) follow-up frequencies, and (4) discontinuation methods. Recommendations were based on Grading Recommendations Assessment, Development, and Evaluation, which included the literature, clinical experience and consensus, patient and parent comfort, and costs. Out of 430 potentially relevant articles, 5 comparative studies were included. Final guideline recommendations were (1) initially observe 3-month-old patients with centered DDH, start abduction treatment if the hip does not normalize after 6-12 weeks; (2) prescribe a Pavlik harness to children <6 months with persisting DDH on repeated ultrasonography, consider alternative abduction devices for children >6 months; (3) assess patients every 6 weeks; and (4) discontinue the abduction device when the hip has normalized or when the child is 12 months. This paper presents a summary of part 1 of the first evidence-based guideline for treatment of centered DDH in children <1 year. Part 2 presents the guideline on decentered DDH in a separate article.

Gepubliceerd: EFORT Open Rev. 2022;7(7):498-505.
Impact factor: 4.775 ; Q1

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14. Increased Speed Elicited More Automatized but Less Predictable Control in Cyclical Arm and Leg Movements
van de Ven WAF, Bosga J, Hullegie W, Verra WC, Meulenbroek RGJ.

The present study explores variations in the degree of automaticity and predictability of cyclical arm and leg movements. Twenty healthy adults were asked to walk on a treadmill at a lower-than-preferred speed, their preferred speed, and at a higher-than-preferred speed. In a separate, repetitive punching task, the three walking frequencies were used to cue the target pace of the cyclical arm movements. Movements of the arms, legs, and trunk were digitized with inertial sensors. Whereas absolute slope values (|β|) of the linear fit to the power spectrum of the digitized movements ($p < .001$, $\eta 2 = .676$) were systematically smaller in treadmill walking than in repetitive punching, sample entropy measures ($p < .001$, $\eta 2 = .570$) were larger reflecting the former task being more automated but also less predictable than the latter task. In both tasks, increased speeds enhanced automatized control ($p < .001$, $\eta 2 = .475$) but reduced movement predictability ($p = .008$,

η2 = .225). The latter findings are potentially relevant when evaluating effects of task demand changes in clinical contexts.

Gepubliceerd: Motor Control. 2022;26(1):15-35.
Impact factor: 1.535 ; Q4

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15. Ten-year results of a prospective cohort of large-head metal-on-metal total hip arthroplasty : a concise follow-up of a previous report
van Lingen CP, Ettema HB, Bosker BH, Verheyen C.

Aims: Large-diameter metal-on-metal (MoM) total hip arthroplasty (THA) has demonstrated unexpected high failure rates and pseudotumour formation. The purpose of this prospective cohort study is to report ten-year results in order to establish revision rate, prevalence of pseudotumour formation, and relation with whole blood cobalt levels**.**
Methods: All patients were recalled according to the guidelines of the Dutch Orthopaedic Association. They underwent clinical and radiographical assessments (x-ray and CT scan) of the hip prosthesis and whole blood cobalt ion measurements. Overall, 94 patients (95 hips) fulfilled our requirements for a minimum ten-year follow-up**.**
Results: Mean follow-up was 10.9 years (10 to 12), with a cumulative survival rate of 82.4%. Reason for revision was predominantly pseudotumour formation (68%), apart from loosening, pain, infection, and osteolysis. The prevalence of pseudotumour formation around the prostheses was 41%, while our previous report of this cohort (with a mean follow-up of 3.6 years) revealed a 39% prevalence. The ten-year revision-free survival with pseudotumour was 66.7% and without pseudotumour 92.4% ($p < 0.05$). There was poor discriminatory ability for cobalt for pseudotumour formation**.**
Conclusion: This prospective study reports a minimum ten-year follow-up of large-head MoM THA. Revision rates are high, with the main reason being the sequelae of pseudotumour formation, which were rarely observed after five years of implantation. Blood ion measurements show limited discriminatory capacity in diagnosing pseudotumour formation. Our results evidence that an early comprehensive follow-up strategy is essential for MoM THA to promptly identify and manage early complications and revise on time. After ten years follow-up, we do not recommend continuing routine CT scanning or whole cobalt blood measurements, but instead enrolling these patients in routine follow-up protocols for THA. Cite this article: Bone Jt Open 2022;3(1):61-67.

Gepubliceerd: Bone Jt Open. 2022;3(1):61-7.
Impact factor: 0; Q NVT

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16. Infection mimicking skin condition: pyoderma gangrenosum
Burlage E, Mulder J, Nellensteijn JM, Zeegers A.

The a priori risk of infection is high when a patient presents with an ulcerative skin condition and elevated inflammatory parameters. If the ulceration is progressive despite adequate antibiotic therapy and tissue cultures are negative, pyoderma gangrenosum should be considered as the diagnosis. This rare infection mimicking skin condition can develop and worsen due to surgery. In this paper, we report two cases that illustrate the importance of making this clinical diagnosis in a timely manner in order to avoid unnecessary surgical interventions and worsening of the clinical picture.

Gepubliceerd: BMJ Case Rep. 2022;15(8).
Impact factor 0.9; Q NVT

Totale impact factor: 37.313
Gemiddelde impact factor: 2.332

Aantal artikelen 1e, 2e of laatste auteur: 8
Totale impact factor: 11.490
Gemiddelde impact factor: 1.640

Pathologie

1. Sex Differences in Neoplastic Progression in Barrett's Esophagus: A Multicenter Prospective Cohort Study
Roumans CAM, Zellenrath PA, Steyerberg EW, Lansdorp-Vogelaar I, Doukas M, Biermann K, Alderliesten J, van Ingen G, Nagengast WB, Karrenbeld A, Ter Borg F, Hage M, Ter Borg PCJ, den Bakker MA, Alkhalaf A, Moll FCP, Brouwer-Hol L, van Baarlen J, Quispel R, van Tilburg A, Burger JPW, van Tilburg AJP, Ooms A, Tang TJ, Romberg-Camps MJL, Goudkade D, Bruno MJ, Rizopoulos D, Spaander MCW.

Recommendations in Barrett's esophagus (BE) guidelines are mainly based on male patients. We aimed to evaluate sex differences in BE patients in (1) probability of and (2) time to neoplastic progression, and (3) differences in the stage distribution of neoplasia. We conducted a multicenter prospective cohort study including 868 BE patients. Cox regression modeling and accelerated failure time modeling were used to estimate the sex differences. Neoplastic progression was defined as high-grade dysplasia (HGD) and/or esophageal adenocarcinoma (EAC). Among the 639 (74%) males and 229 females that were included (median follow-up 7.1 years), 61 (7.0%) developed HGD/EAC. Neoplastic progression risk was estimated to be twice as high among males (HR 2.26, 95% CI 1.11-4.62) than females. The risk of HGD was found to be higher in males (HR 3.76, 95% CI 1.33-10.6). Time to HGD/EAC (AR 0.52, 95% CI 0.29-0.95) and HGD (AR 0.40, 95% CI 0.19-0.86) was shorter in males. Females had proportionally more EAC than HGD and tended to have higher stages of neoplasia at diagnosis. In conclusion, both the risk of and time to neoplastic progression were higher in males. However, females were proportionally more often diagnosed with (advanced) EAC. We should strive for improved neoplastic risk stratification per individual BE patient, incorporating sex disparities into new prediction models.

Gepubliceerd: Cancers (Basel). 2022;14(13).
Impact factor: 6.575; Q1

Totale impact factor: 6.575
Gemiddelde impact factor: 6.575

Aantal artikelen 1e, 2e of laatste auteur: 0
Totale impact factor: 0
Gemiddelde impact factor: 0

Plastische Chirurgie

1. Is Early Active Motion After 3-Ligament Tenodesis Noninferior to Late Active Motion? A Prospective, Multicenter Cohort Study
Bakker D, Colaris JW, Kraan GA, Mathijssen N, Selles R, Smit X, Wouters R, Hand-Wrist Study Group; Blomme RAM.

Purpose: If early active motion after 3-ligament tenodesis is safe, it may yield more patient comfort and an early return to activities. Therefore, the aim of this study was to investigate whether early active motion is noninferior to late active motion after 3-ligament tenodesis for scapholunate interosseous ligament injuries**.**
Methods: This prospective, multicenter cohort study, using a noninferiority design with propensity score matching, compared a late active motion protocol (immobilization for 10-16 days, wrist therapy in weeks 5-6) with an early active motion protocol (immobilization for 3-5 days, wrist therapy during week 2). Patients who were older than 18 years, had complete baseline information on demographics, and underwent 3-ligament tenodesis were included. The outcome measures were postoperative Patient-Reported Wrist/Hand Evaluation scores, pain, complications, return to work, range of motion, grip strength, and satisfaction with treatment results at 3 months of follow-up**.**
Results: After propensity matching, a total of 108 patients were included. Patient-Reported Wrist/Hand Evaluation and pain scores during physical load following an early active motion protocol were noninferior compared with scores following a late active motion protocol. Furthermore, early active motion did not lead to an increase of complications, differences in range of motion or grip strength, or less satisfaction with the treatment result. An earlier return to work was not observed.
Conclusions: Early active motion leads to noninferior results without more complications as compared with late active motion. Based on these findings, early active motion can be considered safe, and might be recommended due to its potential benefits compared with late active motion after 3-ligament tenodesis. TYPE OF STUDY/LEVEL OF EVIDENCE: Therapeutic III.

Gepubliceerd: J Hand Surg Am. 2022;47(11):1076-84.
Impact factor: 2.342 ; Q3

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2. Using a Digital Implant Catalog Improves Data Quality and Reduces Administrative Burden in the Dutch Breast Implant Registry
Barati N, Vrolijk JJ, Becherer BE, van Bommel ACM, Hommes JE, Mureau MAM, van der Hulst R, Young-Afat DA, Rakhorst HA.

Background: Correct registration of implant characteristics is essential to monitor implant safety within implant registries. Currently, in the nationwide Dutch Breast Implant Registry (DBIR), these characteristics are being registered manually by plastic surgeons, resulting in administrative burden and potentially incorrect data entry.
Objectives: This study evaluated the accuracy of manually registered implant data, possible consequences of incorrect data, and the potential of a Digital Implant Catalog (DIC) on increasing data quality and reducing the administrative burden**.**
Methods: Manually entered implant characteristics (fill, shape, coating, texture) of newly inserted breast implants in the DBIR, from 2015 to 2019, were compared with the corresponding implant characteristics in the DIC. Reference numbers were employed to match characteristics between the 2 databases. The DIC was based on manufacturers' product catalogs and set as the gold standard**.**
Results: A total of 57,361 DBIR records could be matched with the DIC. Accuracy of implant characteristics varied from 70.6% to 98.0%, depending on the implant characteristic. The largest discrepancy was observed for "texture" and the smallest for "coating." All manually registered

implant characteristics resulted in different conclusions about implant performance compared with the DIC (P < 0.01). Implementation of the DIC reduced the administrative burden from 14 to 7 variables (50%).
Conclusions: Implementation of a DIC increases data quality in the DBIR and reduces the administrative burden. However, correct registration of reference numbers in the registry by plastic surgeons remains key for adequate matching. Furthermore, all implant manufacturers should be involved, and regular updates of the DIC are required.

Gepubliceerd: Aesthet Surg J. 2022;42(5):Np275-np81.
Impact factor: 4.485 ; Q1

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3. Breast cancer recurrence after immediate and delayed postmastectomy breast reconstruction-A systematic review and meta-analysis
Bargon CA, Young-Afat DA, Ikinci M, Braakenburg A, Rakhorst HA, Mureau MAM, Verkooijen HM, Doeksen A.

Background: Oncological safety of different types and timings of PMBR after breast cancer remains controversial. Lack of stratified risk assessment in literature makes current clinical and shared decision-making complex. This is the first systematic review and meta-analysis to evaluate differences in oncological outcomes after immediate versus delayed postmastectomy breast reconstruction (PMBR) for autologous and implant-based PMBR separately**.**
Methods: A systematic literature search was performed in MEDLINE, Cochrane Library, and Embase. The Cochrane Collaboration Handbook and Meta-analysis Of Observational Studies in Epidemiology checklist were followed for data abstraction. Variability in point estimates attributable to heterogeneity was assessed using I(2) -statistic. (Loco)regional breast cancer recurrence rates, distant metastasis rates, and overall breast cancer recurrence rates were pooled in generalized linear mixed models using random effects**.**
Results: Fifty-five studies, evaluating 14,217 patients, were included. When comparing immediate versus delayed autologous PMBR, weighted average proportions were: 0.03 (95% confidence interval [CI], 0.02-0.03) versus 0.02 (95% CI, 0.01-0.04), respectively, for local recurrences, 0.02 (95% CI, 0.01-0.03) versus 0.02 (95% CI, 0.01-0.03) for regional recurrences, and 0.04 (95% CI, 0.03-0.06) versus 0.01 (95% CI, 0.00-0.03) for locoregional recurrences. No statistically significant differences in weighted average proportions for local, regional and locoregional recurrence rates were observed between immediate and delayed autologous PMBR. Data did not allow comparing weighted average proportions of distant metastases and total breast cancer recurrences after autologous PMBR, and of all outcome measures after implant-based PMBR.
Conclusions: Delayed autologous PMBR leads to similar (loco)regional breast cancer recurrence rates compared to immediate autologous PMBR. This study highlights the paucity of strong evidence on breast cancer recurrence after specific types and timings of PMBR. LAY SUMMERY: Oncologic safety of different types and timings of postmastectomy breast reconstruction (PMBR) remains controversial. Lack of stratified risk assessment in literature makes clinical and shared decision-making complex. This meta-analysis showed that delayed autologous PMBR leads to similar (loco)regional recurrence rates as immediate autologous PMBR. Data did not allow comparing weighted average proportions of distant metastases and total breast cancer recurrence after autologous PMBR, and of all outcome measures after implant-based PMBR. Based on current evidence, oncological concerns do not seem a valid reason to withhold patients from certain reconstructive timings or techniques, and patients should equally be offered all reconstructive options they technically qualify for.

Gepubliceerd: Cancer. 2022;128(19):3449-69.

Impact factor: 6.921; Q1

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4. Variation in the use of infection control measures and infection-related revision incidence after breast implant surgery in the Netherlands
Becherer BE, Marang-van de Mheen PJ, Young-Afat DA, van der Hulst R, Keuter XHA, Rakhorst HA, Mureau MAM.

Background: The use and effect of most infection control measures (ICMs) in breast implant surgery are still debated, likely resulting in undesired variation in current practices.
Objectives: This study investigated the relationship between the number and combinations of ICMs used and the infection-related revision incidence after breast implant surgery. Additionally, national variation between Dutch healthcare institutions in ICM use was evaluated**.**
Methods: For this multicentre, population-based study, all patients who received a primary breast implant or tissue expander for breast augmentation or reconstruction between 2015 and 2019 were identified from the Dutch Breast Implant Registry. Seven prospectively collected ICMs were investigated: preoperative antibiotics, implant and/or pocket irrigation, glove change, nipple guards, insertion sleeve, postoperative drains, and postoperative antibiotics**.**
Results: This study included 52,415 implants (85% augmentation, 15% reconstruction).The median (IQR) number of ICMs used was 3 (3-4) for augmentation and 4 (4-5) for reconstruction. Median follow-up was 30 months for augmentation and 34 months for reconstruction. Infection-related revision incidence was 0.1% for augmentation and 2.1% for reconstruction. Most infection-related revisions occurred within 2 months for augmentation and 2.5 months for reconstruction. The impact of ICM use on infection-related revision incidence remained unclear, given its low incidence. A significant variation was observed between institutions in the use of postoperative antibiotics and drains.
Conclusions: Although the use of different ICMs varied considerably between institutions, the infection-related revision incidence after breast implant surgery was generally low. Most surgeons used four ICMs for breast reconstruction and three ICMs for breast augmentation. Further studies on the causes and effects of the observed variation are needed.

Gepubliceerd: JPRAS Open. 2022;34:226-38.
Impact factor: 0 ; Q NVT

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5. International Lower Limb Collaborative (INTELLECT) study: a multicentre, international retrospective audit of lower extremity open fractures
Berner JE, Chan JKK, Gardiner MD, Navia A, Tejos R, Ortiz-Llorens M, Ortega-Briones A, Rakhorst HA, Nanchahal J, Jain A.

Gepubliceerd: Br J Surg. 2022;109(9):792-5.
Impact factor: 11.782; Q1

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6. Towards evidence based plastic surgery; how a national research agenda can unite research
Bijlard E, Oflazoglu K, Hommes J, Leereveld D, Young-Afat DA, Horbach S, Guitton TG, Hoogbergen MM, Rakhorst HA.

We describe the development of the Research Agenda of the Dutch Society for Plastic Surgery, supported and democratically created by plastic surgeons, patients, and other stakeholders. The agenda contains the 10 most relevant knowledge gaps encountered in clinical practice, as prioritized

by the abovementioned groups. The aim is to stimulate national collaborations and research networks to initiate trials to answer these knowledge gaps. The agenda will be renewed periodically to stay relevant. We encourage other national and international associations to develop a research agenda within their field, and intensify their research network and improve research quality.

Gepubliceerd: J Plast Reconstr Aesthet Surg. 2022;75(1):439-88.
Impact factor: 3.022 ; Q2

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7. Two-Corner Fusion or Four-Corner Fusion of the Wrist for Midcarpal Osteoarthritis? A Multicenter Prospective Comparative Cohort Study
Duraku LS, Hundepool CA, Hoogendam L, Selles RW, van der Heijden B, Colaris JW, Hovius SER, Zuidam JM, Hand-Wrist Study Group; Blomme RAM.

Background: Midcarpal osteoarthritis is a debilitating wrist pain, and a mainstay treatment is midcarpal fusion. The accepted standard for midcarpal fusion is four-corner fusion, but lately, two-corner fusion (i.e., capitolunate fusion) has gained popularity. This is the first prospective, multicenter, cohort study comparing capitolunate fusion with four-corner fusion for midcarpal osteoarthritis**.**
Methods: Patients with scaphoid nonunion advanced collapse or scapholunate advanced collapse wrist of grade 2 to 3 undergoing capitolunate fusion or four-corner fusion between 2013 and 2019 were included. Sixty-three patients (34 with capitolunate fusion, 29 with four-corner fusion) were included. Patient demographics were similar between groups. Patient-Rated Wrist Hand Evaluation questionnaire score, visual analog scale pain score, grip strength, range of motion, and complications were measured at baseline and 3 months and 12 months postoperatively. Complications (i.e., nonunion, hardware migration, conversion to wrist arthrodesis, or arthroplasty) were determined**.**
Results: A significant difference in Patient-Rated Wrist Hand Evaluation or visual analog scale pain score at 3 and 12 months postoperatively between the capitolunate fusion and four-corner fusion groups was not found. There were no differences in grip strength between patient groups preoperatively or 12 months postoperatively. At 12 months postoperatively, capitolunate fusion patients had better flexion compared with that in the four-corner fusion group ($p = 0.002$); there were no differences in complications and reoperation rates between groups.
Conclusions: Capitolunate fusion and four-corner fusion were comparable in terms of functional scores (i.e., Patient-Rated Wrist Hand Evaluation and visual analog scale pain scores) and complication scores. Capitolunate fusion showed favorable wrist mobility compared with four-corner fusion in treatment of midcarpal osteoarthritis. Capitolunate fusion advantages include use of less material, less need for bone-graft harvesting, and easier reduction of the lunate during fixation.
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, II.

Gepubliceerd: Plast Reconstr Surg. 2022;149(6):1130e-9e.
Impact factor: 5.169 ; Q1

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8. ICOPLAST-from infancy to the First World Congress
Evans GRD, Murphy RX, Rakhorst HA, Lessard L, Khashaba A, Kirschbaum JD, Mayer HF.

Gepubliceerd: Eur J Plast Surg. 2022;45(2):365-70.
Impact factor: 0 ; Q NVT

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9. Which Tendon Plasty Has the Best Outcome? A Comparison of Four Tendon Plasty Techniques in a Large Cohort of Patients with Symptomatic Trapeziometacarpal Osteoarthritis
Hoogendam L, Bink T, de Lange J, Selles RW, Colaris JW, Zuidam JM, Hovius SER, van der Heijden B, Hand-Wrist Study Group; Blomme RAM.

Background: Trapeziometacarpal osteoarthritis is commonly treated with a trapeziectomy combined with a form of tendon plasty. The type of tendon plasty used is based on the surgeon's preference. The purpose of this observational study was to compare the outcomes of four different tendon plasties combined with trapeziectomy used to treat osteoarthritis of the trapeziometacarpal joint: the Weilby, Burton-Pellegrini, Zancolli, and anchovy plasty procedures**.**
Methods: Patients treated with a trapeziectomy followed by a tendon plasty completed patient-reported outcome measures at baseline and 12 months postoperatively. The primary outcome was the Michigan Hand Outcomes Questionnaire pain subscale. Secondary outcomes were the minimal clinically important difference of Michigan Hand Outcomes Questionnaire pain scale score, Michigan Hand Outcomes Questionnaire hand function, satisfaction, and complication rate**.**
Results: Seven hundred ninety-three patients underwent a trapeziectomy with a tendon plasty between November of 2013 and December of 2018. There was no difference in pain score after 12 months between the four tendon plasty techniques. Patients undergoing an anchovy plasty had a higher chance of reaching the minimal clinically important difference for Michigan Hand Outcomes Questionnaire pain score compared to the other techniques (OR, 2.3; 95 percent CI, 1.2 to 4.6). Overall, more than 80 percent of the patients were satisfied with the treatment outcome, independent of which technique was used. Complication rates of the different techniques were similar.
Conclusions: Surgical treatment of osteoarthritis of the trapeziometacarpal joint reduced pain after 12 months, independent of which tendon plasty was used. Patients undergoing an anchovy plasty were more likely to experience a clinically relevant improvement in pain while having similar hand function, satisfaction, and complication rates. This suggests that anchovy plasty is the preferred tendon plasty. CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, III.

Gepubliceerd: Plast Reconstr Surg. 2022;150(2):364e-74e.
Impact factor: 5.169 ; Q1

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10. Complications and Functional Outcomes following Trigger Finger Release: A Cohort Study of 1879 Patients
Koopman JE, Hundepool CA, Duraku LS, Smit JM, Zuidam JM, Selles RW, Wouters RM, Hand-Wrist Study Group; Blomme RAM.

Background: Although trigger finger release is considered a safe procedure, large cohort studies reporting consistent complication rates and functional outcomes are scarce. Further insight into outcomes of this commonly performed procedure is essential for adequate treatment evaluation and patient counseling. Therefore, the aim of this study was to assess the complication rates and functional outcomes following trigger finger release**.**
Methods: This is an observational multicenter cohort study of patients undergoing trigger finger release. The primary outcome included the occurrence of complications. The secondary outcome was change in hand function (Michigan Hand outcomes Questionnaire) from baseline to 3 months postoperatively**.**
Results: Complications were observed in 17.1 percent of 1879 patients. Most complications were minor, requiring hand therapy or analgesics (7.0 percent of all patients), antibiotics, or steroid injections (7.8 percent). However, 2.1 percent required surgical treatment and 0.2 percent developed complex regional pain syndrome. The Michigan Hand Outcomes Questionnaire total score improved

from baseline to 3 months postoperatively with 12.7 points, although the authors found considerable variation in outcomes with less improvement in patients with better baseline scores.
Conclusions: This study demonstrates that trigger finger release results in improved hand function, although complications occur in 17 percent. Most complications are minor and can be treated with nonsurgical therapy, resulting in improved hand function as well. However, additional surgical treatment is required in 2 percent of patients. In addition, the authors found that change in hand function depends on the baseline score, with less improvement in patients with better baseline scores. Future studies should investigate factors that contribute to the variability in treatment outcomes following trigger finger release. CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

Gepubliceerd: Plast Reconstr Surg. 2022;150(5):1015-24.
Impact factor: 5.169 ; Q1

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11. Prevalence and Risk Factors for Postoperative Complications Following Open A1 Pulley Release for a Trigger Finger or Thumb
Koopman JE, Zweedijk BE, Hundepool CA, Duraku LS, Smit J, Wouters RM, Selles RW, Zuidam JM, Hand-Wrist Study Group; Blomme RAM.

Purpose: Although A1 pulley release is an effective treatment to reduce pain and improve hand function, complications may occur. More insight into risk factors for complications is essential to improve patient counseling and potentially target modifiable risk factors. This study aimed to identify factors associated with complications following A1 pulley release**.**
Methods: Patients completed baseline questionnaires, including patient characteristics, clinical characteristics, and the Michigan Hand outcomes Questionnaire. We retrospectively reviewed medical records to identify complications classified using the International Consortium for Health Outcome Measurement Complications in Hand and Wrist conditions tool. Grade 1 complications comprise treatment with additional hand therapy, splinting, or analgesics, grade 2 treatment with antibiotics or steroid injections, grade 3A minor surgical treatment, grade 3B major surgical treatment, and grade 3C complex regional pain syndrome. Logistic regression analyses were performed to examine the contribution of patient characteristics, clinical characteristics, and patient-reported outcome measurement scores to complications**.**
Results: Of the included 3,428 patients, 16% incurred a complication. The majority comprised milder grades 1 (6%) and 2 (7%) complications, followed by more severe grades 3B (2%), 3C (0.1%), and 3A (0.1%) complications. A longer symptom duration (standardized odds ratio [SOR], 1.09), ≥3 preoperative steroid injections (SOR, 3.22), a steroid injection within 3 months before surgery (SOR, 2.02), and treatment of the dominant hand (SOR, 1.34), index finger (SOR, 1.65), and middle finger (SOR, 2.01) were associated with a higher complication rate**.**
Conclusion: This study demonstrates that ≥3 preoperative steroid injections and a steroid injection within 3 months before surgery were the most influential factors contributing to complications. These findings can assist clinicians during patient counseling and may guide preoperative treatment. We recommend that clinicians should consider avoiding steroid injections within 3 months before surgery and to be reluctant to perform >2 steroid injections. TYPE OF STUDY/LEVEL OF EVIDENCE: Prognostic II.

Gepubliceerd: J Hand Surg Am. 2022;47(9):823-33.
Impact factor: 2.342 ; Q3

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12. Prevalence of Local Postoperative Complications and Breast Implant Illness in Women With Breast Implants

Lieffering AS, Hommes JE, Ramerman L, Rakhorst HA, Mureau MAM, Verheij RA, van der Hulst R.

Importance: It is unknown how often breast implant illness (BII) is the indication for revision in women with silicone breast implants.
Objective: To examine how often women with silicone breast implants have their implants explanted or replaced because of BII compared with local postoperative complications.
Design, Setting and participants: A legacy cohort study on breast implant revision surgery was conducted between April 1, 2015, and December 31, 2020, and a prospective cohort study on breast implantation and revision surgery was conducted between April 1, 2015, and December 31, 2019 (with follow-up until December 31, 2020). Data were obtained from the Dutch Breast Implant Registry. Data analysis was performed from September 2021 to August 2022. EXPOSURES: Silicone breast implant.
Main Outcomes and Measures: Breast implant revision with the indication BII or local postoperative complications**.**
Results: All 12 882 cosmetic breast implants (6667 women; mean [SD] age, 50.6 [12.7] years) and 2945 reconstructive breast implants (2139 women, mean [SD] age, 57.9 [11.3] years) in the legacy cohort and all 47 564 cosmetic breast implants (24 120 women, mean [SD] age, 32.3 [9.7] years) and 5928 reconstructive breast implants (4688 women, mean [SD] age, 50.9 [11.5] years) in the prospective cohort were included for analysis. In the prospective cohort, 739 cosmetic breast implants (1.6%) were revised after a median (IQR) time to reoperation of 1.8 (0.9-3.1) years, and 697 reconstructive breast implants (11.8%) were revised after a median (IQR) time to reoperation of 1.1 (0.5-1.9) years. BII was registered as the reason for revision in 35 cosmetic revisions (4.7%) and 5 reconstructive revisions (0.7%) in the prospective cohort, corresponding to 0.1% of the inserted implants. In the legacy cohort, 536 cosmetic revisions (4.2%) and 80 reconstructive breast implant revisions (2.7%) were performed because of BII.
Conclusions and Relevance: In this cohort study of women with silicone breast implants, BII was an uncommon indication for revision compared with local complications, both in the short and long term. In contrast to the increasing public interest in BII, these results showed that local complications are a far more common reason for breast implant revision.

Gepubliceerd: JAMA Netw Open. 2022;5(10):e2236519.
Impact factor: 13.360 ; Q1

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13. Outcome of Simple Decompression of Primary Cubital Tunnel Syndrome Based on Patient-Reported Outcome Measurements
Mendelaar NHA, Hundepool CA, Hoogendam L, Duraku LS, Power DM, Walbeehm ET, Selles RW, Zuidam JM, Hand-Wrist Study Group; Blomme RAM.

Purpose: To evaluate the patient-reported outcome measures of patients with primary cubital tunnel syndrome and to assess whether they are affected by preoperative symptom severity**.**
Methods: Patients who underwent simple decompression for primary cubital tunnel syndrome were selected from a prospectively maintained database. Outcome measurements consisted of the Boston Carpal Tunnel Questionnaire at intake and at 3 and 6 months after surgery. Also, 6 months after surgery, the patients received a question about their satisfaction with the treatment result. To determine a possible influence of preoperative symptom severity on postoperative outcomes, the sample was divided into quartiles based on symptom severity at intake**.**
Results: One hundred and forty-five patients were included in the final analysis. On average, all patients improved on the Boston Carpal Tunnel Questionnaire. The subgroup of patients with the mildest symptoms at intake did not improve significantly on symptom severity but did improve significantly on their functional status. In addition, the patients with the most severe symptoms at

intake did improve on both aspects. Moreover, no difference in satisfaction with treatment result between the severity of symptoms at intake was found.
Conclusions: The patients with the mildest symptoms at intake may not improve on symptom severity, but they do improve on functional status after simple decompression for cubital tunnel syndrome. In addition, patients with the most severe symptoms at intake do improve on both symptom severity and functional status. Moreover, all patients reported to be equally satisfied with the treatment result, which suggests that satisfaction is not dependent on the symptom severity at intake. Even those patients with both the mildest symptoms before surgery and the least improvement still seem to benefit from simple decompression. TYPE OF STUDY/LEVEL OF EVIDENCE: Therapeutic IV.

Gepubliceerd: J Hand Surg Am. 2022;47(3):247-56.e1.
Impact factor: 2.342 ; Q3

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14. ESPRAS Survey on Continuing Education in Plastic, Reconstructive and Aesthetic Surgery in Europe
Moellhoff N, Arnez T, Athanasopoulos E, Costa H, De Santis G, De Mortillet S, Demirdöver C, Benedetto GD, Dzonov B, Elander A, Hansson E, Henley M, Jecan CR, Kaartinen I, Karabeg R, Kharkov A, Kneafsey B, Gjorgova ST, Palencar D, Portincasa A, Psaras G, Rakhorst H, Alonso MER, Rouif M, Saboye J, Pompeo FSD, Spendel S, Stepic N, Vasar O, Zic R, Giunta RE.

Background: Specialty training in plastic, reconstructive and aesthetic surgery is a prerequisite for safe and effective provision of care. The aim of this study was to assess and portray similarities and differences in the continuing education and specialization in plastic surgery in Europe.
Material and Methods: A detailed questionnaire was designed and distributed utilizing an online survey administration software. Questions addressed core items regarding continuing education and specialization in plastic surgery in Europe. Participants were addressed directly via the European Leadership Forum (ELF) of the European Society of Plastic, Reconstructive and Aesthetic Surgery (ESPRAS). All participants had detailed knowledge of the organization and management of plastic surgical training in their respective country**.**
Results: The survey was completed by 29 participants from 23 European countries. During specialization, plastic surgeons in Europe are trained in advanced tissue transfer and repair and aesthetic principles in all parts of the human body and within several subspecialties. Moreover, rotations in intensive as well as emergency care are compulsory in most European countries. Board certification is only provided for surgeons who have had multiple years of training regulated by a national board, who provide evidence of individually performed operative procedures in several anatomical regions and subspecialties, and who pass a final oral and/or written examination**.**
Conclusion: Board certified plastic surgeons meet the highest degree of qualification, are trained in all parts of the body and in the management of complications. The standard of continuing education and qualification of European plastic surgeons is high, providing an excellent level of plastic surgical care throughout Europe.

Gepubliceerd: Handchir Mikrochir Plast Chir. 2022;54(4):365-73.
Impact factor: 0.985 ; Q4

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15. Dorsal Subluxation of the Proximal Interphalangeal Joint After Volar Base Fracture of the Middle Phalanx
Oflazoglu K, de Planque CA, Guitton TG, Rakhorst H, Chen NC.

Background: Treatment decisions regarding volar base fractures of the middle phalanx depend on whether the proximal interphalangeal (PIP) joint is reduced. Our aim was to study the agreement among hand surgeons in determining whether the PIP joint fractures are subluxated and to study the factors associated with subluxation of these fractures**.**
Methods: In this retrospective chart review, 413 volar base fractures of the middle phalanx were included. Demographic and injury-related factors were gathered from medical records and radiographs. Using a Web-based survey, interobserver agreement was determined among 105 hand surgeons on the assessment of PIP joint subluxation of a series of 26 cases. Using the cohort of 413 fractures, a threshold for percent articular involvement and relative fracture displacement that corresponds with subluxation of the PIP joint was analyzed**.**
Results: We found moderate to substantial agreement between hand surgeons on subluxation (κ = 0.59, P < .0001) and an overall percent agreement of 85%. Percent articular involvement and relative fracture displacement were independently associated with subluxation of the PIP joint (P < .001). Percent articular involvement of 35% had a specificity of 90% and a negative predicting value (NPV) of 92% for joint subluxation. Relative fracture displacement of 35% had a specificity of 92% and an NPV of 94% for joint subluxation**.**
Conclusions: Surgeons generally agree on whether a PIP joint is subluxated. Percent articular involvement and relative fragment displacement are objective measurements that can help characterize joint stability and assist with decision-making.

Gepubliceerd: Hand (N Y). 2022;17(1):60-7.
Impact factor: 0 ; Q NVT

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16. Bradford Hill and breast implant illness: no evidence for causal association with breast implants
Spoor J, de Jong D, de Boer M, Rakhorst H, van der Hulst R, Vrancken Peeters M, Bleiker EMA, Mureau MAM, van Leeuwen FE.

Gepubliceerd: Expert Rev Clin Immunol. 2022;18(8):773-5.
Impact factor: 5.124 ; Q2

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17. Return to Usual Work Following an Ulnar Shortening Osteotomy: A Sample of 111 Patients
Teunissen JS, Feitz R, Al Shaer S, Hovius S, Selles RW, Van der Heijden B, Hand-Wrist Study Group; Blomme RAM.

Purpose: The primary aim of this study was to analyze the median time until patients performed their usual work following an ulnar shortening osteotomy (USO). The secondary aim was to identify factors influencing the median time until return to their usual work**.**
Methods: We used a retrospective cohort of patients with ongoing data collection from our institution in the Netherlands. Patients with paid employment who underwent USO were invited to complete a return-to-work questionnaire at 6 weeks, 3 months, 6 months, and 12 months after surgery. The probability of and median time until return to usual work were assessed using an inverted Kaplan-Meier analysis. Factors influencing the return to usual work were evaluated using multivariable Cox proportional hazard regression**.**
Results: In total, 111 patients who underwent USO were included, with a mean age of 46 years. The probability of returning to usual work in the first year was 92%, and the median time was 12 weeks. The type of work was independently associated with a return to work, with median times of 8, 12, and 14 weeks for light, moderate, and heavy physical work, respectively. We did not find differences in return to usual work based on age, sex, duration of complaints until surgery, treatment side,

smoking status, the preoperative Patient-Rated Wrist Evaluation score, or whether the osteotomy was performed freehand or with an external cutting device.
Conclusions: Half of the patients that underwent USO fully performed their usual work by 12 weeks following surgery. We found that 92% of the patients performed their usual work within 1 year after surgery. We found a large variation in the time until a return to work based on the type of work. Surgeons can use this data to inform patients on the rehabilitation phase after USO.

Gepubliceerd: J Hand Surg Am. 2022;47(8):794.e1-.e11.
Impact factor: 2.342 ; Q3

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18. Outcomes of ulna shortening osteotomy: a cohort analysis of 106 patients
Teunissen JS, Wouters RM, Al Shaer S, Zöphel OT, Vermeulen GM, Hovius SER, Van der Heijden EPA, Hand-Wrist Study Group; Blomme RAM.

Background: Ulna shortening osteotomy (USO) for ulnar impaction syndrome (UIS) aims to improve pain and function by unloading the ulnar carpus. Previous studies often lack validated patient-reported outcomes or have small sample sizes. The primary objective of this study was to investigate patient-reported pain and hand function at 12 months after USO for UIS. Secondary objectives were to investigate the active range of motion, grip strength, complications, and whether outcomes differed based on etiology.
Material and Methods: We report on 106 patients with UIS who received USO between 2012 and 2019. In 44 of these patients, USO was performed secondary to distal radius fracture. Pain and function were measured with the Patient Rated Wrist/Hand Evaluation (PRWHE) before surgery and at 3 and 12 months after surgery. Active range of motion and grip strength were measured before surgery and at 3 and 12 months after surgery. Complications were scored using the International Consortium for Health Outcome Measurement Complications in Hand and Wrist conditions (ICHAW) tool**.**
Results: The PRWHE total score improved from a mean of 64 (SD = 18) before surgery to 40 (22) at 3 months and 32 (23) at 12 months after surgery ($P < 0.001$; effect size Cohen's d = -1.4). There was no difference in the improvement in PRWHE total score (P = 0.99) based on etiology. Also, no clinically relevant changes in the active range of motion were measured. Independent of etiology, mean grip strength improved from 24 (11) before surgery to 30 (12) at 12 months ($P = 0.001$). Sixty-four percent of patients experienced at least one complication, ranging from minor to severe. Of the 80 complications in total, 50 patients (47%) had complaints of hardware irritation, of which 34 (32%) had their hardware removed. Six patients (6%) needed refixation because of nonunion**.**
Conclusion: We found beneficial outcomes in patients with UIS that underwent USO, although there was a large variance in the outcome and a relatively high number of complications (which includes plate removals). Results of this study may be used in preoperative counseling and shared decision-making when considering USO. LEVEL OF EVIDENCE: Therapeutic III.

Gepubliceerd: J Orthop Traumatol. 2022;23(1):1.
Impact factor: 4.239 ; Q1

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19. Autologous lipoaspirate as a new treatment of vulvar lichen sclerosus: A review on literature
van der Sluis N, Scheers E, Krenning G, van der Lei B, Oonk MHM, van Dongen JA.

Lichen sclerosus (LS) is a chronic inflammatory dermatosis that mostly affects the genital and anal skin areas. Symptoms may vary from pruritis and pain to sexual dysfunction; however, LS can also be asymptomatic. LS occurs at all ages and in both sexes. Approximately 5% of all women affected by

vulvar LS will develop vulvar squamous cell carcinoma. Topical treatment is safe but less effective resulting in chronic course in most patients, who suffer from persistent itching and pain. In severe cases of therapy-resistant LS, there is no adequate treatment. Fat grafting is a novel regenerative therapy to reduce dermal fibrosis. The therapeutic effect of adipose tissue grafts for LS is already investigated in various pioneering studies. This review provides an overview of these studies and the putative mechanisms-of-action of fat grafting to treat LS.

Gepubliceerd: Exp Dermatol. 2022;31(5):689-99.
Impact factor: 4.511 ; Q1

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20. A neonate with a facial congenital pressure injury: a case report
van der Sluis N, Theodora Wilhelmina Ten Hoope B, Bosch T, Wiesman ME, Schmidbauer U, Rakhorst HA.

This is the first case report of a facial congenital pressure injury in a full-term neonate, due to pressure on the neonate's head between a large leiomyoma and the mother's pelvic bone.

Gepubliceerd: Case Reports Plast Surg Hand Surg. 2022;9(1):88-91.
Impact factor: 0 ; Q NVT

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21. Predictors of delayed breast reconstruction in the Netherlands: a 5-year follow-up study in stage I-III breast cancer patients
van Egdom LSE, de Ligt KM, de Munck L, Koppert LB, Mureau MAM, Rakhorst HA, Siesling S.

Purpose: Delayed breast reconstruction (DBR) is a valid option for postmastectomy breast cancer patients who have a desire for breast reconstruction but are not considered suitable for immediate breast reconstruction (IBR). The objective of this study was to investigate the clinical practice and predictors of the use of DBR in the Netherlands**.**
Methods: Stage I-III breast cancer patients diagnosed from January to March 2012 and treated with mastectomy were selected from the Netherlands Cancer Registry. Routinely collected patient, tumor, treatment and hospital characteristics were complemented with data about DBR up to 2018. Multivariable logistic regression analyses were performed to identify factors independently associated with postmastectomy DBR. Factors associated with time to DBR were identified through Cox regression analyses**.**
Results: Of all patients who underwent mastectomy (n = 1,415), 10.2% underwent DBR. DBR patients more often received autologous reconstruction compared to IBR patients (37.5% vs 6.2%, $p < 0.001$). Age below 50 years (age < 35 OR 15.55, age 35-49 OR 4.18) and neoadjuvant and adjuvant chemotherapy (OR 2.59 and OR 2.83, respectively) were significantly associated with DBR. Mean time to DBR was 2.4 years [range 1-6 years]. Time to DBR was significantly associated with age < 35 years (HR 2.22), and a high hospital volume (HR 1.87).
Discussion: The use of DBR after mastectomy could not be fully explained by age below 50 years, chemotherapy, and hospital volume. Treatment with radiotherapy and adjuvant chemotherapy increased time to DBR. More information about patient preferences is needed to understand the use and timing of reconstruction.

Gepubliceerd: Breast Cancer. 2022;29(2):324-35.
Impact factor: 3.307; Q2

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22. Development of guidelines for the management of patients with open fractures: The potential cost-savings of international collaboration
Verheul E, Berner JE, Oflazoglu K, Troisi L, Arnež Z, Ortega-Briones A, Nanchahal J, Rakhorst H.

Gepubliceerd: J Plast Reconstr Aesthet Surg. 2022;75(1):439-88.
Impact factor: 3.022 ; Q2

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23. Comparing costs of standard Breast-Conserving Surgery to Oncoplastic Breast-Conserving Surgery and Mastectomy with Immediate two-stage Implant-Based Breast Reconstruction
Witmer TJK, Kouwenberg CAE, Bargon CA, de Leeuw DM, Koiter E, Siemerink EJM, Mureau MAM, Rakhorst HA.

Background: Conventional breast-conserving surgery (C-BCS) has equal oncological outcomes and superior cosmetic and patient-reported outcomes compared to mastectomy with immediate two-stage implant-based breast reconstruction (M-IBR). Oncoplastic breast-conserving surgery (OP-BCS) is increasingly being used, as it often has better cosmetic results and it enables larger tumour resection. However, OP-BCS and M-IBR compared to C-BCS lengthens operative time and might lead to more complications and consequently to additional costs. Therefore, this study aimed to compare costs and complication rates of C-BCS, OP-BCS and M-IBR**.**
Methods: This single-centre, retrospective cohort study, calculated costs for all patients who had undergone breast cancer surgery between January 2014 and December 2016. Patient-, tumour- and surgery-related data of C-BCS, OP-BCS and M-IBR patients were retrieved by medical record review. Treatment costs were calculated using hospital financial data. Differences in costs and complications were analysed**.**
Results: A total of 220 patients were included: 74 patients in the C-BCS, 78 in the OP-BCS and 68 in the M-IBR group. From most expensive to least expensive, differences in total costs were found between C-BCS vs. OP-BCS and C-BCS vs. M-IBR (p=<0.01 and p=0.04, respectively). Costs of OP-BCS and M-IBR were comparable. Complication rates were 5.5% for C-BCS, followed by 17% for OP-BCS, and 34% for M-IBR (p<0.01)**.**
Conclusion: Considering total treatment costs, OP-BCS was financially non-inferior to M-IBR, whereas complication rates were higher following M-IBR. Therefore, when considering other benefits of OP-BCS, such as higher patient-reported outcomes and similar oncological outcomes, a shift from M-IBR to BCS using oncoplastic techniques seems justified.

Gepubliceerd: J Plast Reconstr Aesthet Surg. 2022;75(8):2569-76.
Impact factor: 3.022 ; Q2

Totale impact factor: 88.655
Gemiddelde impact factor: 3.855

Aantal artikelen 1e, 2e of laatste auteur: 6
Totale impact factor: 18.062
Gemiddelde impact factor: 3.010

Raad van Bestuur

1. Patient preference attributes in eHealth interventions for cancer-related fatigue: A scoping review
Beenhakker L, Witteveen A, Wijlens KAE, Siemerink EJM, van der Lee ML, Bode C, Siesling S, Vollenbroek-Hutten MMR.

Introduction: Cancer-related fatigue (CRF) is one of the most reported long-term effects breast cancer patients experience after diagnosis. Many interventions for CRF are effective, however, not for every individual. Therefore, intervention advice should be adjusted to patients' preferences and characteristics. Our aim was to develop an overview of eHealth interventions and their (preference sensitive) attributes**.**
Methods: eHealth interventions were identified using a scoping review approach. Eligible studies included breast cancer patients and assessed CRF as outcome. Interventions were categorised as physical activity, mind-body, psychological, 'other' or 'combination'. Information was extracted on various (preference sensitive) attributes, like duration, intensity, peer support and costs**.**
Results: Thirty-five interventions were included and divided over the intervention categories. (Preference sensitive) attributes varied both within and between these categories. Duration varied from 4 weeks to 6 months, intensity from daily to own pace. Peer support was present in seven interventions and costs were known for six**.**
Conclusion: eHealth interventions exist in various categories, additionally, there is much variation in (preference sensitive) attributes. This provides opportunities to implement our overview for personalised treatment recommendations for breast cancer patients struggling with CRF. Taking into account patients' preferences and characteristics suits the complexity of CRF and heterogeneity of patients.

Gepubliceerd: Eur J Cancer Care (Engl). 2022;31(6):e13754.
Impact factor: 2.328 ; Q2

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2. Implementation of a pneumonia prevention protocol to decrease the incidence of postoperative pneumonia in patients after hip fracture surgery
Geerds MAJ, Folbert EC, Visschedijk SFM, Klunder MB, Vollenbroek-Hutten MMR, Hegeman JH.

Objective: Postoperative pneumonia is among the most common complications in elderly patients after hip fracture surgery. We implemented a proactive postoperative pneumonia prevention protocol and analyzed the incidence of postoperative pneumonia in elderly patients (≥70 years of age) receiving this protocol after hip fracture surgery versus those receiving usual care before the protocol's implementation at our institution.
Material and Methods: From November 2018 to October 2019, the proactive postoperative pneumonia prevention protocol was implemented. The treatment included intensified physical therapy, postoperative pulmonary exercises and oral care, in addition to the usual surgical treatment for elderly patients with hip fracture. The intervention cohort data were compared with a historical control cohort treated from July 2017 to June 2018. The primary outcome of this study was the incidence of postoperative pneumonia in both groups, diagnosed according to the presence of two of three of the following: elevated infection parameters, radiologic examination confirmation of pneumonia of the chest or clinical suspicion**.**
Results: A total of 494 patients (n= 249 in the historical control cohort and n=245 in the intervention cohort) were included. A total of 69 patients developed postoperative pneumonia. The incidence of postoperative pneumonia was significantly lower (6.7 percentage points) in the group receiving the proactive postoperative pneumonia prevention protocol (17.3% in the historical control cohort vs

10.6% in the intervention cohort; p=0.033). DISCUSSION AND CONCLUSION: A proactive postoperative pneumonia prevention protocol showed promise in decreasing the occurrence of postoperative pneumonia after hip fracture surgery in elderly patients.

Gepubliceerd: Injury. 2022;53(8):2818-22.
Impact factor: 2.687 ; Q2

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3. The Need for Objective Physical Activity Measurements in Routine Bariatric Care
Kuipers E, Timmerman J, van Det M, Vollenbroek-Hutten M.

Purpose: This study aims to (1) quantify physical behavior through self-reports and sensor-based measures, (2) examine the correlation between self-reported and sensor-based physical activity (PA) and (3) assess whether bariatric patients adhere to PA guidelines**.**
Methods: A Fitbit accelerometer was used to collect minute-to-minute step count and heart rate data for 14 consecutive days. Total physical activity levels (PAL), moderate-to-vigorous intensity physical activity (MVPA) and sedentary behavior (SB) were used to quantify physical behavior. Self-reported PA was assessed with the International Physical Activity Questionnaire (IPAQ). To analyze the association between sensor-based and self-reported PA, Spearman's correlation was used. A minimum of 150 MVPA minutes per week was considered as compliance with the PA guidelines**.**
Results: Fitbit data of 37 pre- and 18 post-surgery patients was analyzed. Participants averaged 7403 ± 3243 steps/day and spent most of their time sedentary (832 min, IQR: 749 - 879), especially in prolonged periods of ≥ 30 min (525, IQR: 419 - 641). Median MVPA time was 5.6 min/day (IQR: 1.7 - 10.6). Correlations between self-reported and sensor-based MVPA and SB were respectively 0.072 and 0.455. Only 17.1% was objectively adherent to MVPA guidelines ≥ 150 min/week, while 94.3% met the guidelines in case of self-reports**.**
Conclusion: PA quantification confirmed that bariatric patients are highly sedentary and rarely engage in MVPA, despite a relatively high daily step count. Moreover, bariatric patients are not able to assess MVPA and moderately their SB by self-reports. Our results indicate the need for sensor-based PA monitoring in routine bariatric care.

Gepubliceerd: Obes Surg. 2022;32(9):2975-86.
Impact factor: 3.479 ; Q2

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4. Patient compliance with postoperative precautions in an unrestricted and a supine sleeping position following posterolateral total hip arthroplasty: a randomized controlled trial
Peters A, Manning F, Tijink M, Vollenbroek-Hutten M, Huis In 't Veld R.

Purpose: To evaluate compliance with the precaution to sleep in a supine position following total hip arthroplasty (THA) and its impact on the other precautions.
Material and Methods: Single-center, parallel-group, stratified, randomized trial. Patients were allocated to a Restricted Group or an Unrestricted Group. This study focuses on compliance with the precaution to sleep in a supine position, compliance with the remaining set of precautions and the burden of restricted sleeping. Measurements were made using a self-administered diary and questionnaires. Trial registration number: NCT02107248**.**
Results: During the first 2 weeks, 81% of the patients in the restricted group were compliant with sleeping in a supine position.Patients in the Unrestricted Group significantly kept sleeping fewer days per week in a supine position than patients in the Restricted Group (p = 0.000). No significant differences between the two groups were found regarding compliance with the remaining set of

precautions. The burden of the sleeping restriction is significantly lowered in the Unrestricted Group (p = 0.000).
Conclusions: Compliance with restricting patients to sleep in a supine position is high. Removing this precaution has a significant decrease in burden for patients without affecting compliance with the remaining set of precautions.
Trial registration number: ClinicalTrials.gov NCT02107248 –
Implications for rehabilitation: Sleeping precautions cause a high rate of burden to patients, whereas movement precautions do not. By removing sleeping precautions, the burden is significantly reduced without affecting the remaining set of precautions. Compliance with movement precautions is high compared to other more functional precautions.

Gepubliceerd: Disabil Rehabil. 2022;44(26):8303-10.
Impact factor: 2.439; Q2

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5. Geriatric Syndromes and Incident Chronic Health Conditions Among 9094 Older Community-Dwellers: Findings from the Lifelines Cohort Study
Rausch C, van Zon SKR, Liang Y, Laflamme L, Möller J, de Rooij SE, Bültmann U.

Objectives: To determine the association between geriatric syndromes and any specific incident chronic health conditions among older community-dwellers.
Design: Population-based cohort study over a median follow-up period of 43 months. SETTING AND PARTICIPANTS: Participants from the Lifelines Cohort Study aged 60 years and older without presence of the studied chronic health conditions at baseline (n = 9094)**.**
Methods: Baseline assessment took place between November 2006 and December 2013 and included information on socioeconomic (age, sex, level of education and income), social contact, and health-related factors [eg, self-rated health, body mass index, chronic health conditions, and health behavior (alcohol consumption and smoking)]. Participants also reported the presence of geriatric syndromes (ie, included falls, incontinence, vision impairment, hearing impairment, depressive symptoms, and frailty at baseline). Three follow-up questionnaires were used to examine the incidence of any and specific chronic health conditions (ie, pulmonary and cardiovascular diseases, diabetes, cancer, and neurological diseases). Cox regression was used to analyze the longitudinal associations between geriatric syndromes and incident chronic health conditions**.**
Results: Older community-dwelling individuals with at least one geriatric syndrome (44.7%, n = 4038) had an increased risk of developing any new chronic health condition [hazard ratio (HR) 1.35; 95% confidence interval (CI) 1.21-1.51]. The association was attenuated but remained significant after adjustment for socioeconomic factors, social contact, health status, and health behavior (HR 1.27; 95% CI 1.12-1.43). Analyses for specific chronic health conditions showed that compared with older community-dwellers without geriatric syndromes, those with geriatric syndromes had an increased risk to develop a cardiovascular health condition (HR 1.42; 95% CI 1.13-1.79) or diabetes (HR 1.53; 95% CI 1.11-2.11). They had no increased risk to develop pulmonary conditions, cancer, or neurological conditions.
Conclusion and implications: The presence of geriatric syndromes is associated with incident chronic health conditions, specifically cardiovascular conditions and diabetes. Increased awareness is needed among older people with geriatric syndromes and their physicians. Comprehensive assessments of geriatric syndromes may help to prevent or at least delay the development of chronic health conditions.

Gepubliceerd: J Am Med Dir Assoc. 2022;23(1):54-9.e2.
Impact factor: 7.802 ; Q1

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6. What web-based intervention for chronic cancer-related fatigue works best for whom? Explorative moderation analyses of a randomized controlled trial
Schellekens MPJ, Bruggeman-Everts FZ, Wolvers MDJ, Vollenbroek-Hutten MMR, van der Lee ML.

Purpose: Approximately 25% of cancer patients suffer from chronic cancer-related fatigue (CCRF), which is a complex, multifactorial condition. While there are evidence-based interventions, it remains unclear what treatment works best for the individual patient. This study explored whether baseline characteristics moderated the effect of web-based mindfulness-based cognitive therapy (eMBCT) versus ambulant activity feedback (AAF) and a psycho-education control group (PE) on fatigue in patients suffering from CCRF**.**
Methods: In a randomized controlled trial, participant suffering from CCRF participated in either eMBCT, AAF, or PE. Complete data of the treatment-adherent sample (≥ 6 sessions) was used to explore whether sociodemographic, clinical, and psychological characteristics at baseline moderated the intervention effect on fatigue severity at 6 months**.**
Results: A trend showed that baseline fatigue severity and fatigue catastrophizing moderated the intervention effect. That is, at low levels of fatigue severity and catastrophizing, patients benefited more from AAF than from eMBCT and at high levels of fatigue severity and catastrophizing, patients benefited more from eMBCT than from PE.
Conclusions: This study found some preliminary evidence on what treatment works best for the individual suffering from CCRF. These findings emphasize the potential gain in effectiveness of personalizing treatment. An alternative approach that might help us further in answering the question "what treatment works best for whom?" is discussed.

Gepubliceerd: Support Care Cancer. 2022;30(10):7885-92.
Impact factor: 3.359 ; Q1

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7. Early identification of frailty: Developing an international delphi consensus on pre-frailty
Sezgin D, O'Donovan M, Woo J, Bandeen-Roche K, Liotta G, Fairhall N, Rodríguez-Laso A, Apóstolo J, Clarnette R, Holland C, Roller-Wirnsberger R, Illario M, Mañas LR, Vollenbroek-Hutten M, Doğu BB, Balci C, Pernas FO, Paul C, Ahern E, Romero-Ortuno R, Molloy W, Cooney MT, O'Shea D, Cooke J, Lang D, Hendry A, Kennelly S, Rockwood K, Clegg A, Liew A, O'Caoimh R.

Background: Frailty is associated with a prodromal stage called pre-frailty, a potentially reversible and highly prevalent intermediate state before frailty becomes established. Despite being widely-used in the literature and increasingly in clinical practice, it is poorly understood.
Objective: To establish consensus on the construct and approaches to diagnose and manage pre-frailty**.**
Methods: We conducted a modified (electronic, two-round) Delphi consensus study. The questionnaire included statements concerning the concept, aspects and causes, types, mechanism, assessment, consequences, prevention and management of pre-frailty. Qualitative and quantitative analysis methods were employed. An agreement level of 70% was applied**.**
Results: Twenty-three experts with different backgrounds from 12 countries participated. In total, 70 statements were circulated in Round 1. Of these, 52.8% were accepted. Following comments, 51 statements were re-circulated in Round 2 and 92.1% were accepted. It was agreed that physical and non-physical factors including psychological and social capacity are involved in the development of pre-frailty, potentially adversely affecting health and health-related quality of life. Experts considered pre-frailty to be an age-associated multi-factorial, multi-dimensional, and non-linear process that does not inevitably lead to frailty. It can be reversed or attenuated by targeted interventions. Brief,

feasible, and validated tools and multidimensional assessment are recommended to identify pre-frailty.
Conclusions: Consensus suggests that pre-frailty lies along the frailty continuum. It is a multidimensional risk-state associated with one or more of physical impairment, cognitive decline, nutritional deficiencies and socioeconomic disadvantages, predisposing to the development of frailty. More research is needed to agree an operational definition and optimal management strategies.

Gepubliceerd: Arch Gerontol Geriatr. 2022;99:104586.
Impact factor: 4.163 ; Q2

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8. An ideographic study into physiology, alcohol craving and lapses during one hundred days of daily life monitoring
van Lier HG, Noordzij ML, Pieterse ME, Postel MG, Vollenbroek-Hutten MMR, de Haan HA, Schraagen JMC.

Introduction: Alcohol craving is a highly challenging obstacle to achieve long-term abstinence. Making alcohol use disorder patients timely aware of high-risk craving situations may protect them against relapse by prompting them to mobilize their coping resources. Current advances in wearable and smart-phone technology provide novel opportunities for the development of detecting these situations of heightened risk of craving, by enabling continuous tracking of fluctuations in psychological and physiological parameters. The present study therefore aims to determine the association between self-reported craving and relapses, and between heightened physiological activity. Specifically, we measured cardiovascular and electrodermal activity, and self-reported craving during one hundred days in the daily life of people trying to recover from alcoholism. The secondary aim is to study whether the association between physiology and craving can be strengthened by the inclusion of context related psychological parameters**.**
Methods: An intensive repeated and continuous measures in naturalistic settings case-study design was employed. Ten participants were monitored with wearable bio-sensors and answered multiple questions every three hours on a smartphone app about craving, lapsing and multiple evidence based contextual variables. The association between physiology, craving and lapses was explored using Matthews correlation coefficients both with a current and 3 h lagged design. The contextual variables were included in a decision tree together with the physiological parameters to explore the added effect on the correlation of these contextual variables**.**
Results: The association between lapses and craving was highly different across individuals, varying between a weak to a strong association. The association between cardiovascular activity and heightened self-reported craving was negligible to weak, however with a high specificity, meaning that most craving events were accompanied by increase heart rate. However, the association between electrodermal activity and craving was lower than with cardiovascular activity for most participants, both prior (lagged) and during craving. For two of the participants the association between physiology and craving improved by adding contextual variables, however, precision was too low.
Conclusions: People differ strongly in their bodily reactions and psychological experiences during the first months of their addiction treatment. No individual in our study had unique one-to-one mappings between on the one hand physiological or psychological precursors, and on the other hand craving and (re)lapses. Therefore, detecting high risk craving situations with both physiological activity measured with wearables and psychological precursors to alert people specifically for an imminent (re)lapse, does not seem viable on the basis of the current results. We do see an added benefit of using physiology during treatment, as physiology can help start the conversation about possible high risk craving situations during that week. This would also help the counselor to gain added insights into the fluctuating states of the clients, and help to ameliorate the recall bias of

clients. The present study showed the possibility and paved the way for future intensive longitudinal designs integrating both physiological, psychological and contextual factors during the challenging and lengthy recovery from addiction.

Gepubliceerd: Addict Behav Rep. 2022;16:100443.
Impact factor: 0; Q NVT

Totale impact factor: 26.257
Gemiddelde impact factor: 3.282

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 5.807
Gemiddelde impact factor: 2.904

Radiologie

1. Impact of the lockdown on acute stroke treatments during the first surge of the COVID-19 outbreak in the Netherlands
Benali F, Stolze LJ, Rozeman AD, Dinkelaar W, Coutinho JM, Emmer BJ, Gons RAR, Yo LFS, van Tuijl JH, Boukrab I, van Dam-Nolen DHK, van den Wijngaard IR, Lycklama À Nijeholt GJ, de Laat KF, van Dijk LC, den Hertog HM, Flach HZ, Wermer MJH, van Walderveen MAA, Brouwers P, Bulut T, Vermeer SE, Bernsen MLE, Uyttenboogaart M, Bokkers RPH, Boogaarts JD, de Leeuw FE, van der Worp HB, van der Schaaf IC, Schonewille WJ, Vos JA, Remmers MJM, Imani F, Dippel DWJ, van Zwam WH, Nederkoorn PJ, van Oostenbrugge RJ.

Introduction: We investigated the impact of the Corona Virus Disease 2019 (COVID-19) pandemic and the resulting lockdown on reperfusion treatments and door-to-treatment times during the first surge in Dutch comprehensive stroke centers. Furthermore, we studied the association between COVID-19-status and treatment times**.**
Methods: We included all patients receiving reperfusion treatment in 17 Dutch stroke centers from May 11th, 2017, until May 11th, 2020. We collected baseline characteristics, National Institutes of Health Stroke Scale (NIHSS) at admission, onset-to-door time (ODT), door-to-needle time (DNT), door-to-groin time (DGT) and COVID-19-status at admission. Parameters during the lockdown (March 15th, 2020 until May 11th, 2020) were compared with those in the same period in 2019, and between groups stratified by COVID-19-status. We used nationwide data and extrapolated our findings to the increasing trend of EVT numbers since May 2017**.**
Results: A decline of 14% was seen in reperfusion treatments during lockdown, with a decline in both IVT and EVT delivery. DGT increased by 12 min (50 to 62 min, p-value of < 0.001). Furthermore, median NIHSS-scores were higher in COVID-19 - suspected or positive patients (7 to 11, p-value of 0.004), door-to-treatment times did not differ significantly when stratified for COVID-19-status.
Conclusions: During the first surge of the COVID-19 pandemic, a decline in acute reperfusion treatments and a delay in DGT was seen, which indicates a target for attention. It also appeared that COVID-19-positive or -suspected patients had more severe neurologic symptoms, whereas their EVT-workflow was not affected.

Gepubliceerd: BMC Neurol. 2022;22(1):22.
Impact factor: 2.903 ; Q3

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2. Breast MRI in patients after breast conserving surgery with sentinel node procedure using a superparamagnetic tracer
Christenhusz A, Pouw JJ, Simonis FFJ, Douek M, Ahmed M, Klaase JM, Dassen AE, Klazen CAH, van der Schaaf MC, Ten Haken B, Alic L.

Background: A procedure for sentinel lymph node biopsy (SLNB) using superparamagnetic iron-oxide (SPIO) nanoparticles and intraoperative sentinel lymph node (SLN) detection was developed to overcome drawbacks associated with the current standard-of-care SLNB. However, residual SPIO nanoparticles can result in void artefacts at follow-up magnetic resonance imaging (MRI) scans. We present a grading protocol to quantitatively assess the severity of these artefacts and offer an option to minimise the impact of SPIO nanoparticles on diagnostic imaging**.**
Methods: Follow-up mammography and MRI of two patient groups after a magnetic SLNB were included in the study. They received a 2-mL subareolar dose of SPIO (high-dose, HD) or a 0.1-mL intratumoural dose of SPIO (low-dose, LD). Follow-up mammography and MRI after magnetic SLNB were acquired within 4 years after breast conserving surgery (BCS). Two radiologists with over 10-

year experience in breast imaging assessed the images and analysed the void artefacts and their impact on diagnostic follow-up**.**
Results: A total of 19 patients were included (HD, n = 13; LD, n = 6). In the HD group, 9/13 patients displayed an artefact on T1-weighted images up to 3.6 years after the procedure, while no impact of the SPIO remnants was observed in the LD group.
Conclusions: SLNB using a 2-mL subareolar dose of magnetic tracer in patients undergoing BCS resulted in residual artefacts in the breast in the majority of patients, which may hamper follow-up MRI. This can be avoided by using a 0.1-mL intratumoural dose.

Gepubliceerd: Eur Radiol Exp. 2022;6(1):3.
Impact factor: 0 ; Q NVT

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3. Improvements in Endovascular Treatment for Acute Ischemic Stroke: A Longitudinal Study in the MR CLEAN Registry
Compagne KCJ, Kappelhof M, Hinsenveld WH, Brouwer J, Goldhoorn RB, Uyttenboogaart M, Bokkers RPH, Schonewille WJ, Martens JM, Hofmeijer J, van der Worp HB, Lo RTH, Keizer K, Yo LSF, Lycklama À Nijeholt GJ, den Hertog HM, Sturm EJC, Brouwers P, van Walderveen MAA, Wermer MJH, de Bruijn SF, van Dijk LC, Boogaarts HD, van Dijk EJ, van Tuijl JH, Peluso JPP, de Kort PLM, van Hasselt B, Fransen PS, Schreuder T, Heijboer RJJ, Jenniskens SFM, Sprengers MES, Ghariq E, van den Wijngaard IR, Roosendaal SD, Meijer A, Beenen LFM, Postma AA, van den Berg R, Yoo AJ, van Doormaal PJ, van Proosdij MP, Krietemeijer MGM, Gerrits DG, Hammer S, Vos JA, Boiten J, Coutinho JM, Emmer BJ, van Es A, Roozenbeek B, Roos Y, van Zwam WH, van Oostenbrugge RJ, Majoie C, Dippel DWJ, van der Lugt A.

Background: We evaluated data from all patients in the Netherlands who underwent endovascular treatment for acute ischemic stroke in the past 3.5 years, to identify nationwide trends in time to treatment and procedural success, and assess their effect on clinical outcomes**.**
Methods: We included patients with proximal occlusions of the anterior circulation from the second and first cohorts of the MR CLEAN (Multicenter Randomized Clinical trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry (March 2014 to June 2016; June 2016 to November 2017, respectively). We compared workflow times and rates of successful reperfusion (defined as an extended Thrombolysis in Cerebral Infarction score of 2B-3) between cohorts and chronological quartiles (all included patients stratified in chronological quartiles of intervention dates to create equally sized groups over the study period). Multivariable ordinal logistic regression was used to assess differences in the primary outcome (ordinal modified Rankin Scale at 90 days)**.**
Results: Baseline characteristics were similar between cohorts (second cohort n=1692, first cohort n=1488) except for higher age, poorer collaterals, and less signs of early ischemia on computed tomography in the second cohort. Time from stroke onset to groin puncture and reperfusion were shorter in the second cohort (median 185 versus 210 minutes; P<0.001 and 236 versus 270 minutes; P<0.001, respectively). Successful reperfusion was achieved more often in the second than in the first cohort (72% versus 66%; P<0.001). Functional outcome significantly improved (adjusted common odds ratio 1.23 [95% CI, 1.07-1.40]). This effect was attenuated by adjustment for time from onset to reperfusion (adjusted common odds ratio, 1.12 [95% CI, 0.98-1.28]) and successful reperfusion (adjusted common odds ratio, 1.13 [95% CI, 0.99-1.30]). Outcomes were consistent in the analysis per chronological quartile.
Conclusions: Clinical outcomes after endovascular treatment for acute ischemic stroke in routine clinical practice have improved over the past years, likely resulting from improved workflow times and higher successful reperfusion rates.

Gepubliceerd: Stroke. 2022;53(6):1863-72.

Impact factor: 10.170 ; Q1

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4. A multicenter prospective cohort study to evaluate feasibility of radio-frequency identification surgical guidance for nonpalpable breast lesions: design and rationale of the RFID Localizer 1 Trial
den Dekker BM, Christenhusz A, van Dalen T, Jongen LM, van der Schaaf MC, Dassen AE, Pijnappel RM.

Background: Breast cancer screening and improving imaging techniques have led to an increase in the detection rate of early, nonpalpable breast cancers. For early breast cancer, breast conserving surgery is an effective and safe treatment. Accurate intraoperative lesion localization during breast conserving surgery is essential for adequate surgical margins while sparing surrounding healthy tissue to achieve optimal cosmesis. Preoperative wire localization and radioactive seed localization are accepted standard methods to guide surgical excision of nonpalpable breast lesions. However, these techniques present significant limitations. Radiofrequency identification (RFID) technology offers a new, nonradioactive method for localizing nonpalpable breast lesions in patients undergoing breast conserving surgery. This study aims to evaluate the feasibility of RFID surgical guidance for nonpalpable breast lesions**.**
Methods: This multicenter prospective cohort study was approved by the Institutional Review Board of the University Medical Center Utrecht. Written informed consent is obtained from all participants. Women with nonpalpable, histologically proven in situ or invasive breast cancer, who can undergo breast conserving surgery with RFID localization are considered eligible for participation. An RFID tag is placed under ultrasound guidance, up to 30 days preoperatively. The surgeon localizes the RFID tag with a radiofrequency reader that provides audible and visual real-time surgical guidance. The primary study outcome is the percentage of irradical excisions and reexcision rate, which will be compared to standards of the National Breast Cancer Organisation Netherlands (NABON)(≤ 15% irradical excisions of invasive carcinomas). Secondary outcomes include user acceptability/experiences, learning curve, duration and ease of the placement- and surgical procedure and adverse events.
Discussion: This study evaluates the feasibility of RFID surgical guidance for nonpalpable breast lesions. Results may have implications for the future localization techniques in women with nonpalpable breast cancer undergoing breast conserving surgery.
Trial registration: Netherlands National Trial Register, NL8019 , registered on September 12(th) 2019.

Gepubliceerd: BMC Cancer. 2022;22(1):305.
Impact factor: 4.638 ; Q2

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5. Hospital Variation in Time to Endovascular Treatment for Ischemic Stroke: What Is the Optimal Target for Improvement?
den Hartog SJ, Lingsma HF, van Doormaal PJ, Hofmeijer J, Yo LSF, Majoie C, Dippel DWJ, van der Lugt A, Roozenbeek B, MR CLEAN Registry investigators; Brouwers PJAM, Gerrits D.

Background: Time to reperfusion in patients with ischemic stroke is strongly associated with functional outcome and may differ between hospitals and between patients within hospitals. Improvement in time to reperfusion can be guided by between-hospital and within-hospital comparisons and requires insight in specific targets for improvement. We aimed to quantify the variation in door-to-reperfusion time between and within Dutch intervention hospitals and to assess the contribution of different time intervals to this variation**.**
Methods and Results: We used data from the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry. The door-to-

reperfusion time was subdivided into time intervals, separately for direct patients (door-to-computed tomography, computed tomography-to-computed tomography angiography [CTA], CTA-to-groin, and groin-to-reperfusion times) and for transferred patients (door-to-groin and groin-to-reperfusion times). We used linear mixed models to distinguish the variation in door-to-reperfusion time between hospitals and between patients. The proportional change in variance was used to estimate the amount of variance explained by each time interval. We included 2855 patients of 17 hospitals providing endovascular treatment. Of these patients, 44% arrived directly at an endovascular treatment hospital. The between-hospital variation in door-to-reperfusion time was 9%, and the within-hospital variation was 91%. The contribution of case-mix variables on the variation in door-to-reperfusion time was marginal (2%-7%). Of the between-hospital variation, CTA-to-groin time explained 83%, whereas groin-to-reperfusion time explained 15%. Within-hospital variation was mostly explained by CTA-to-groin time (33%) and groin-to-reperfusion time (42%). Similar results were found for transferred patients**.**
Conclusions: Door-to-reperfusion time varies between, but even more within, hospitals providing endovascular treatment for ischemic stroke. Quality of stroke care improvements should not only be guided by between-hospital comparisons, but also aim to reduce variation between patients within a hospital, and should specifically focus on CTA-to-groin time and groin-to-reperfusion time.

Gepubliceerd: J Am Heart Assoc. 2022;11(1):e022192.
Impact factor: 6.107 ; Q2

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6. Predictive Factors for Sustained Pain after (sub)acute Osteoporotic Vertebral Fractures. Combined Results from the VERTOS II and VERTOS IV Trial
Firanescu CE, Venmans A, de Vries J, Lodder P, Schoemaker MC, Smeets AJ, Donga E, Juttmann JR, Schonenberg K, Klazen CAH, Elgersma OEH, Jansen FH, Fransen H, Hirsch JA, Lohle PNM.

Purpose: Osteoporotic vertebral compression fractures are treated conservatively or in selected cases with percutaneous vertebroplasty (PV). The purpose of this retrospective analysis is to determine predictive factors for a high visual analogue scale (VAS) pain score after conservative, sham or PV and is based on previously published randomized trials**.**
Methods: The VERTOS II compared conservative versus PV, and VERTOS IV compared sham versus PV treatment. The conservative group received pain medication. The sham and PV group received subcutaneous lidocaine/bupivacaine. In addition, the PV group received cementation, which was simulated in the sham group. Nineteen different predictors of high (≥ 5) versus low (< 5) VAS pain score at 12 months were investigated**.**
Results: 20.7% of patients in the PV group demonstrated a VAS ≥ 5 at the 12-month, compared to 40.1% in the conservative or sham group, with a significant difference ($\chi(2)(1) = 15.26$, $p < 0.0001$, OR = 2.57, 95% CI = 1.59 to 4.15). In the subgroup analysis, we detected five predictors for the risk of high pain scores (VAS ≥ 5 after 12 months follow-up), namely: female, baseline VAS > 8, long-term baseline pain, mild/severe Genant and new fractures.
Conclusions: Statistically significant more patients had a high pain score at 12 months in the sham and conservative group when compared with the PV group. Five predictors were identified for sustained high local back pain, regardless of the received treatment. Patients with moderate fracture deformity were less likely to have high pain scores at 12 months if they received PV than if they had sham or conservative therapy.

Gepubliceerd: Cardiovasc Intervent Radiol. 2022;45(9):1314-21.
Impact factor: 2.797; Q3

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7. Susceptibility-Weighted MRI and Microbleeds in Mild Traumatic Brain Injury: Prediction of Posttraumatic Complaints?
Hageman G, Hof J, Nihom J.

Background: Only in 7-15% of patients with mild traumatic brain injury (mTBI), traumatic CT-abnormalities are found. Nevertheless, 40% of mTBI patients suffer from posttraumatic complaints not resolving after 6 months. We discuss the ability of susceptibility-weighted imaging (SWI), sensitive for microbleeds, to detect more subtle brain abnormalities.
Summary: After a search on PubMed, we selected 15 studies on SWI in adult mTBI patients; 11 studies on 3T MRI, and 4 studies on 1.5T MRI. All 1.5T studies showed that, compared to T2, gradient echo, diffusion-weighted imaging, or fluid-attenuated inversion recovery sequences, SWI is more sensitive for microbleeds. Only two 1.5T studies described the association between SWI findings and outcome. In 3 of the 4 studies, no control group was present. The mean number of microbleeds varied from 3.2 to 6.4 per patient. In the 3T studies, the percentage of patients with traumatic microbleeds varied from 5.7 to 28.8%, compared to 0-13.3% in normal controls. Microbleeds were particularly located subcortical or juxtacortical. The number of microbleeds in mTBI varied from 1 to 10 per patient. mTBI patients with microbleeds appeared to have higher symptom severity at 12 months and perform worse on tests of psychomotor speed and speed of information processing after 3 and 12 months, compared to mTBI patients without microbleeds.
Key messages: There is some evidence that traumatic microbleeds predict cognitive outcome and persistent posttraumatic complaints in patients with mTBI.

Gepubliceerd: Eur Neurol. 2022;85(3):177-85.
Impact factor: 2.292 ; Q4

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8. A Multimodality Myocardial Perfusion Phantom: Initial Quantitative Imaging Results
Kamphuis ME, Kuipers H, Liefers HR, van Es J, Simonis FFJ, Greuter MJW, Slump CH, Slart R.

This proof-of-concept study explores the multimodal application of a dedicated cardiac flow phantom for ground truth contrast measurements in dynamic myocardial perfusion imaging with CT, PET/CT, and MRI. A 3D-printed cardiac flow phantom and flow circuit mimics the shape of the left ventricular cavity (LVC) and three myocardial regions. The regions are filled with tissue-mimicking materials and the flow circuit regulates and measures contrast flow through LVC and myocardial regions. Normal tissue perfusion and perfusion deficits were simulated. Phantom measurements in PET/CT, CT, and MRI were evaluated with clinically used hardware and software. The reference arterial input flow was 4.0 L/min and myocardial flow 80 mL/min, corresponding to myocardial blood flow (MBF) of 1.6 mL/g/min. The phantom demonstrated successful completion of all processes involved in quantitative, multimodal myocardial perfusion imaging (MPI) applications. Contrast kinetics in time intensity curves were in line with expectations for a mimicked perfusion deficit (38 s vs. 32 s in normal tissue). Derived MBF in PET/CT and CT led to under- and overestimation of reference flow of 0.9 mL/g/min and 4.5 mL/g/min, respectively. Simulated perfusion deficit (0.8 mL/g/min) in CT resulted in MBF of 2.8 mL/g/min. We successfully performed initial, quantitative perfusion measurements with a dedicated phantom setup utilizing clinical hardware and software. These results showcase the multimodal phantom's potential.

Gepubliceerd: Bioengineering (Basel). 2022;9(9).
Impact factor: 5.046 ; Q2

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9. Cost Effectiveness of Splenic Artery Embolization versus Splenectomy after Trauma in the Netherlands
Kanters TA, Raaijmakers C, Lohle PNM, de Vries J, Hakkaart-van Roijen L, SPLENIQ study group: de Wit RJ, Klazen CAH.

Purpose: To demonstrate that splenic artery embolization (SAE) is more cost-effective than splenectomy from a societal perspective in the Netherlands.
Material and Methods: Patient-level data obtained from the SPLENIQ study were used to populate a health economic model and were supplemented with expert opinion when necessary. Propensity score matching was used to correct for baseline differences in injury severity scores. The health economic model consisted of 3 health states (complications after intervention, SAE failure, and recovery) and a dead state. Model outcomes were incremental quality-adjusted life years (QALYs) and incremental costs of SAE over splenectomy. The Dutch health economic guidelines were followed. The model used a lifetime time horizon. Uncertainty was assessed using probabilistic sensitivity analysis and scenario analyses**.**
Results: Patients undergoing SAE had a higher life expectancy than patients undergoing splenectomy. Incremental QALYs were 3.1 (mostly explained by difference in life expectancy), and incremental costs were €34,135 (explained by costs related to medical consumption and lost productivity in additional life years), leading to an incremental cost-effectiveness ratio of €11,010 per QALY. SAE was considered cost-effective in >95% of iterations using a threshold of €20,000 per QALY.
Conclusions: SAE results in more QALYs than splenectomy. Intervention costs for SAE are lower than that for splenectomy, but medical consumption and productivity costs in later years are higher for SAE due to better survival. SAE was found to be cost-effective compared with splenectomy under appropriate Dutch cost-effectiveness thresholds.

Gepubliceerd: J Vasc Interv Radiol. 2022;33(4):392-8.e4.
Impact factor: 3.682 ; Q2

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10. A Comprehensive Grading System for a Magnetic Sentinel Lymph Node Biopsy Procedure in Head and Neck Cancer Patients
Nieuwenhuis ER, Kolenaar B, Hof JJ, van Baarlen J, van Bemmel AJM, Christenhusz A, Scheenen TWJ, Ten Haken B, de Bree R, Alic L.

A magnetic sentinel lymph node biopsy ((SLN)B) procedure has recently been shown feasible in oral cancer patients. However, a grading system is absent for proper identification and classification, and thus for clinical reporting. Based on data from eight complete magnetic SLNB procedures, we propose a provisional grading system. This grading system includes: (1) a qualitative five-point grading scale for MRI evaluation to describe iron uptake by LNs; (2) an ex vivo count of resected SLN with a magnetic probe to quantify iron amount; and (3) a qualitative five-point grading scale for histopathologic examination of excised magnetic SLNs. Most SLNs with iron uptake were identified and detected in level II. In this level, most variance in grading was seen for MRI and histopathology; MRI and medullar sinus were especially highly graded, and cortical sinus was mainly low graded. On average 82 ± 58 µg iron accumulated in harvested SLNs, and there were no significant differences in injected tracer dose (22.4 mg or 11.2 mg iron). In conclusion, a first step was taken in defining a comprehensive grading system to gain more insight into the lymphatic draining system during a magnetic SLNB procedure.

Gepubliceerd: Cancers (Basel). 2022;14(3).
Impact factor: 6.575; Q1

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11. Etiology of Large Vessel Occlusion Posterior Circulation Stroke: Results of the MR CLEAN Registry

Pirson F, Boodt N, Brouwer J, Bruggeman AAE, Hinsenveld WH, Staals J, van Zwam WH, van der Leij C, Brans RJB, Majoie C, Dippel DWJ, van der Lugt A, Schonewille WJ, van Oostenbrugge RJ, MR CLEAN Registry Investigators; Brouwers PJAM, Gerrits D.

Background: In patients with large vessel occlusion stroke of the anterior circulation, underlying cause is a determinant of outcome. Whether this is the case for posterior circulation large vessel occlusion stroke has yet to be determined. We aimed to report on cause in patients with posterior circulation stroke treated with endovascular thrombectomy and to analyze the association with functional outcome**.**
Methods: We used data of patients with posterior circulation stroke included in the MR CLEAN (Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) registry, a prospective multicenter observational study, between 2014 and 2018. Stroke cause was categorized into large artery atherosclerosis (LAA), cardioembolism, arterial dissection, embolic stroke of undetermined source (ESUS), other determined cause, or undetermined cause. For primary analysis on the association between cause and outcome, we used multivariable ordinal logistic regression analysis to estimate the adjusted common odds ratio for a shift towards a better functional outcome on the modified Rankin Scale at 90 days with LAA as a reference group. Secondary outcomes included favorable functional outcome (modified Rankin Scale score 0-3), National Institutes of Health Stroke Scale score at 24 to 48 hours, reperfusion on digital subtraction angiography, and stroke progression**.**
Results: Of 264 patients with posterior circulation stroke, 84 (32%) had LAA, 48 (18%) cardioembolism, 31 (12%) dissection, and 14 (5%) ESUS. Patients with a dissection were younger (48 [interquartile range, 43-60] years) and had a lower National Institutes of Health Stroke Scale at baseline (12 [interquartile range, 6-31]) than patients with other cause. Functional outcome was better for patients with cardioembolism and ESUS compared to LAA (modified Rankin Scale adjusted common odds ratio, 2.4 [95% CI, 1.1-5.2], respectively adjusted common odds ratio, 3.1 [95% CI, 1.0-9.3]). Patients with a dissection had a lower chance of successful reperfusion compared with LAA (adjusted odds ratio, 0.20 [95% CI, 0.06-0.70]).
Conclusions: Unlike the anterior circulation, most frequent cause in our posterior large vessel occlusion stroke cohort is LAA followed by cardioembolism, dissection, and ESUS. Patients with cardioembolism and ESUS have a better prognosis for functional outcome after endovascular thrombectomy than patients with LAA.

Gepubliceerd: Stroke. 2022;53(8):2468-77.
Impact factor: 10.170 ; Q1

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12. Endovascular Treatment for Posterior Circulation Stroke in Routine Clinical Practice: Results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands Registry

Pirson FAV, Boodt N, Brouwer J, Bruggeman AAE, den Hartog SJ, Goldhoorn RB, Langezaal LCM, Staals J, van Zwam WH, van der Leij C, Brans RJB, Majoie C, Coutinho JM, Emmer BJ, Dippel DWJ, van der Lugt A, Vos JA, van Oostenbrugge RJ, Schonewille WJ, MR CLEAN Registry Investigators; Brouwers PJAM, Gerrits D.

Background and Purpose: The benefit of endovascular treatment (EVT) for posterior circulation stroke (PCS) remains uncertain, and little is known on treatment outcomes in clinical practice. This study evaluates outcomes of a large PCS cohort treated with EVT in clinical practice. Simultaneous to

this observational study, several intervention centers participated in the BASICS trial (Basilar Artery International Cooperation Study), which tested the efficacy of EVT for basilar artery occlusion in a randomized setting. We additionally compared characteristics and outcomes of patients treated outside BASICS in trial centers to those from nontrial centers**.**
Methods: We included patients with PCS from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands Registry: a prospective, multicenter, observational study of patients who underwent EVT in the Netherlands between 2014 and 2018. Primary outcome was a score of 0 to 3 on the modified Rankin Scale at 90 days. Secondary outcomes included reperfusion status and symptomatic intracranial hemorrhage. For outcome comparison between patients treated in trial versus nontrial centers, we used ordinal logistic regression analysis**.**
Results: We included 264 patients of whom 135 (51%) had received intravenous thrombolysis. The basilar artery was most often involved (77%). Favorable outcome (modified Rankin Scale score 0-3) was observed in 115/252 (46%) patients, and 109/252 (43%) patients died. Successful reperfusion was achieved in 178/238 (75%), and symptomatic intracranial hemorrhage occurred in 9/264 (3%). The 154 nontrial patients receiving EVT in BASICS trial centers had similar characteristics and outcomes as the 110 patients treated in nontrial centers (modified Rankin Scale adjusted cOR: 0.77 [95% CI, 0.5-1.2]).
Conclusions: Our study shows that high rates of favorable clinical outcome and successful reperfusion can be achieved with EVT for PCS, despite high mortality. Characteristics and outcomes of patients treated in trial versus nontrial centers were similar indicating that our cohort is representative of clinical practice in the Netherlands. Randomized studies using modern treatment approaches are needed for further insight in the benefit of EVT for PCS.

Gepubliceerd: Stroke. 2022;53(3):758-68.
Impact factor: 10.170 ; Q1

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13. Effect of Intravenous Alteplase Treatment on First-Line Stent Retriever Versus Aspiration Alone During Endovascular Treatment
Rinkel LA, Treurniet KM, Nieboer D, Kappelhof M, LeCouffe NE, Bruggeman AAE, van Zwam WH, Lycklama ANGJ, Ghariq E, Uyttenboogaart M, Dippel DWJ, Roos Y, Coutinho JM, Majoie C, Emmer BJ, MR CLEAN-NO IV Investigators; Brouwers PJAM, Gerrits D.

Background: We aimed to assess whether the effect of intravenous alteplase treatment (IVT) before endovascular treatment (EVT) on outcome is modified by first-line technique during EVT in IVT eligible patients**.**
Methods: This was a post hoc analysis from MR CLEAN-NO IV (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands - Intravenous Treatment Followed by Intra-Arterial Treatment Versus Direct Intra-Arterial Treatment for Acute Ischemic Stroke Caused by a Proximal Intracranial Occlusion), a randomized trial of IVT followed by EVT versus EVT alone in patients presenting directly to EVT-capable centers. We included data from all patients who underwent EVT with a thrombectomy attempt. We compared patients treated with stent retriever (with or without aspiration) to aspiration alone as first-line EVT technique and assessed the interaction of first-line EVT technique with IVT treatment. Primary outcome was the 90-day modified Rankin Scale score, analyzed with mixed model ordinal regression for a shift towards better outcome. Secondary outcomes included successful reperfusion (extended Thrombolysis in Cerebral Infarction score 2b-3)**.**
Results: Of 473 included patients, 102 (21.6%) were treated with aspiration alone as first-line technique. In the full population, functional outcome was similar for patients treated with stent retriever versus aspiration only (adjusted common odds ratio [acOR]' 1.07 [95% CI, 0.69-1.66]). We

observed a significant interaction between IVT and first-line EVT technique (P=0.03). In the aspiration-only group, patients treated with EVT alone had worse functional outcome compared to those treated with IVT and EVT (acOR, 0.44 [95% CI, 0.21-0.90]). In the stent retriever group, functional outcome did not differ between patients treated with or without IVT (acOR, 1.08 [95% CI, 0.74-1.57]). There was no statistically significant interaction for successful reperfusion.
Conclusions: In MR CLEAN-NO IV, the treatment effect of IVT was modified by first-line EVT technique. Patients treated with aspiration only as first-line technique had worse clinical outcomes if they did not receive IVT. No such difference was observed in patients treated with stent retrievers. Confirmation by pooling with results from other trials is needed to confirm these findings.

Gepubliceerd: Stroke. 2022;53(11):3278-88.
Impact factor: 10.170 ; Q1

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14. Predictors of poor outcome despite successful endovascular treatment for ischemic stroke: results from the MR CLEAN Registry
van de Graaf RA, Samuels N, Chalos V, Lycklama ANGJ, van Beusekom H, Yoo AJ, van Zwam WH, Majoie C, Roos Y, van Doormaal PJ, Ben Hassen W, van der Lugt A, Dippel DWJ, Lingsma HF, van Es A, Roozenbeek B, MR CLEAN Registry investigators; Brouwers PJAM, Gerrits D.

Background: Approximately one-third of patients with ischemic stroke treated with endovascular treatment do not recover to functional independence despite rapid and successful recanalization. We aimed to quantify the importance of predictors of poor functional outcome despite successful reperfusion**.**
Methods: We analyzed patients from the MR CLEAN Registry between March 2014 and November 2017 with successful reperfusion (extended Thrombolysis In Cerebral Infarction ≥2B). First, predictors were selected based on expert opinion and were clustered according to acquisition over time (ie, baseline patient factors, imaging factors, treatment factors, and postprocedural factors). Second, several models were constructed to predict 90-day functional outcome (modified Rankin Scale (mRS)). The relative importance of individual predictors in the most extensive model was expressed by the proportion of unique added χ(2) to the model of that individual predictor**.**
Results: Of 3180 patients, 1913 (60%) had successful reperfusion. Of these 1913 patients, 1046 (55%) were functionally dependent at 90 days (mRS >2). The most important predictors for mRS were baseline patient factors (ie, pre-stroke mRS, added χ(2) 0.16; National Institutes of Health Stroke Scale score at baseline, added χ(2) 0.12; age, added χ(2) 0.10), and postprocedural factors (ie, symptomatic intracranial hemorrhage (sICH), added χ(2) 0.12; pneumonia, added χ(2) 0.09). The probability of functional independence for a typical stroke patient with sICH was 54% (95% CI 36% to 72%) lower compared with no sICH, and 21% (95% CI 4% to 38%) for pneumonia compared with no pneumonia**.**
Conclusion: Baseline patient factors and postprocedural adverse events are important predictors of poor functional outcome in successfully reperfused patients with ischemic stroke. This implies that prevention of postprocedural adverse events has the greatest potential to further improve outcomes in these patients.

Gepubliceerd: J Neurointerv Surg. 2022;14(7):660-5.
Impact factor: 8.572 ; Q1

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15. Economic Evaluation of Endovascular Treatment for Acute Ischemic Stroke

van den Berg LA, Berkhemer OA, Fransen PSS, Beumer D, Lingsma H, Majoie CBM, Dippel DWJ, van der Lugt A, van Oostenbrugge RJ, van Zwam WH, Roos YB, Dijkgraaf MGW, MR CLEAN Investigators; Gerrits D.

Background and Purpose: Endovascular treatment for acute ischemic stroke has been proven clinically effective, but evidence of the cost-effectiveness based on real-world data is scarce. The aim of this study was to assess whether endovascular therapy plus usual care is cost-effective in comparison to usual care alone in acute ischemic stroke patients.
Methods: An economic evaluation was performed from a societal perspective with a 2-year time horizon. Empirical data on health outcomes and the use of resources following endovascular treatment were gathered parallel to the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) and its 2-year follow-up study. Incremental cost-effectiveness ratios were calculated as the extra costs per additional patient with functional independence (modified Rankin Scale score 0-2) and the extra cost per quality-adjusted life year gained.
Results: The mean costs per patient in the intervention group were $126 494 versus $143 331 in the control group (mean difference, -$16 839 [95% CI, -$38 113 to $5456]). Compared with patients in the control group, more patients in the intervention group achieved functional independence, 37.2% versus 23.9% (absolute difference, 13.3% [95% CI, 4.0%-22.0%]) and they generated more quality-adjusted life years, 0.99 versus 0.83 (mean difference of 0.16 [95% CI, 0.04-0.29]). Endovascular treatment dominated standard treatment with $18 233 saved per extra patient with a good outcome and $105 869 saved per additional quality-adjusted life year.
Conclusions: Endovascular treatment added to usual care is clinically effective, and cost saving in comparison to usual care alone in patients with acute ischemic stroke. Registration: URL: https://www.trialregister.nl/trial/695;
Unique identifier: NL695. URL: https://www.isrctn.com;
Unique identifier: ISRCTN10888758.

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Impact factor: 10.170 ; Q1

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16. Added Value of a Blinded Outcome Adjudication Committee in an Open-Label Randomized Stroke Trial

van der Ende NAM, Roozenbeek B, Berkhemer OA, Koudstaal PJ, Boiten J, van Dijk EJ, Roos Y, van Oostenbrugge RJ, Majoie C, van Zwam W, Lingsma HF, van der Lugt A, Dippel DWJ, MR CLEAN Investigators; Gerrits D.

Background and Purpose: Blinded outcome assessment in trials with prospective randomized open blinded end point design is challenging. Unblinding can result in misclassified outcomes and biased treatment effect estimates. An outcome adjudication committee assures blinded outcome assessment, but the added value for trials with prospective randomized open blinded end point design and subjective outcomes is unknown. We aimed to assess the degree of misclassification of modified Rankin Scale (mRS) scores by a central assessor and its impact on treatment effect estimates in a stroke trial with prospective randomized open blinded end point design.
Methods: We used data from the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands). The primary outcome was the mRS at 90 days. Standardized, algorithm-based telephone interviews to assess the mRS were conducted from a central location by an experienced research nurse, unaware but not formally blinded to treatment allocation (central assessor). Masked reports of these interviews were adjudicated by a blinded outcome committee. Misclassification was defined as an incorrect classification of the mRS by the

central assessor. The effect of endovascular treatment on the mRS was assessed with multivariable ordinal logistic regression.
Results: In MR CLEAN, 53/500 (10.6%) of the mRS scores were misclassified. The degree and direction of misclassification did not differ between treatment arms (P=0.59). Benefit of endovascular treatment was shown on the mRS when scored by the central assessor (adjusted common odds ratio, 1.60 [95% CI, 1.16-2.21]) and the outcome adjudication committee (adjusted common odds ratio, 1.67 [95% CI, 1.21-2.20]).
Conclusions: Misclassification by the central assessor was small, randomly distributed over treatment arms, and did not affect treatment effect estimates. This study suggests that the added value of a blinded outcome adjudication committee is limited in a stroke trial with prospective randomized open blinded end point design applying standardized, algorithm-based outcome assessment by a central assessor, who is unaware but not formally blinded to treatment allocation.
Registration: URL: https://www.isrctn.com;
Unique identifier: ISRCTN10888758.

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Impact factor: 10.170 ; Q1

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17. Safety and efficacy of aspirin, unfractionated heparin, both, or neither during endovascular stroke treatment (MR CLEAN-MED): an open-label, multicentre, randomised controlled trial
van der Steen W, van de Graaf RA, Chalos V, Lingsma HF, van Doormaal PJ, Coutinho JM, Emmer BJ, de Ridder I, van Zwam W, van der Worp HB, van der Schaaf I, Gons RAR, Yo LSF, Boiten J, van den Wijngaard I, Hofmeijer J, Martens J, Schonewille W, Vos JA, Tuladhar AM, de Laat KF, van Hasselt B, Remmers M, Vos D, Rozeman A, Elgersma O, Uyttenboogaart M, Bokkers RPH, van Tuijl J, Boukrab I, van den Berg R, Beenen LFM, Roosendaal SD, Postma AA, Krietemeijer M, Lycklama G, Meijer FJA, Hammer S, van der Hoorn A, Yoo AJ, Gerrits D, Truijman MTB, Zinkstok S, Koudstaal PJ, Manschot S, Kerkhoff H, Nieboer D, Berkhemer O, Wolff L, van der Sluijs PM, van Voorst H, Tolhuisen M, Roos Y, Majoie C, Staals J, van Oostenbrugge RJ, Jenniskens SFM, van Dijk LC, den Hertog HM, van Es A, van der Lugt A, Dippel DWJ, Roozenbeek B, MR CLEAN-MED investigators; Brouwers PJAM.

Background: Aspirin and unfractionated heparin are often used during endovascular stroke treatment to improve reperfusion and outcomes. However, the effects and risks of anti-thrombotics for this indication are unknown. We therefore aimed to assess the safety and efficacy of intravenous aspirin, unfractionated heparin, both, or neither started during endovascular treatment in patients with ischaemic stroke.
Methods: We did an open-label, multicentre, randomised controlled trial with a 2 × 3 factorial design in 15 centres in the Netherlands. We enrolled adult patients (ie, ≥18 years) with ischaemic stroke due to an intracranial large-vessel occlusion in the anterior circulation in whom endovascular treatment could be initiated within 6 h of symptom onset. Eligible patients had a score of 2 or more on the National Institutes of Health Stroke Scale, and a CT or MRI ruling out intracranial haemorrhage. Randomisation was done using a web-based procedure with permuted blocks and stratified by centre. Patients were randomly assigned (1:1) to receive either periprocedural intravenous aspirin (300 mg bolus) or no aspirin, and randomly assigned (1:1:1) to receive moderate-dose unfractionated heparin (5000 IU bolus followed by 1250 IU/h for 6 h), low-dose unfractionated heparin (5000 IU bolus followed by 500 IU/h for 6 h), or no unfractionated heparin. The primary outcome was the score on the modified Rankin Scale at 90 days. Symptomatic intracranial haemorrhage was the main safety outcome. Analyses were based on intention to treat, and treatment effects were expressed as odds ratios (ORs) or common ORs, with adjustment for baseline prognostic factors. This trial is registered with the International Standard Randomised Controlled Trial Number, ISRCTN76741621.

Findings: Between Jan 22, 2018, and Jan 27, 2021, we randomly assigned 663 patients; of whom, 628 (95%) provided deferred consent or died before consent could be asked and were included in the modified intention-to-treat population. On Feb 4, 2021, after unblinding and analysis of the data, the trial steering committee permanently stopped patient recruitment and the trial was stopped for safety concerns. The risk of symptomatic intracranial haemorrhage was higher in patients allocated to receive aspirin than in those not receiving aspirin (43 [14%] of 310 vs 23 [7%] of 318; adjusted OR 1·95 [95% CI 1·13-3·35]) as well as in patients allocated to receive unfractionated heparin than in those not receiving unfractionated heparin (44 [13%] of 332 vs 22 [7%] of 296; 1·98 [1·14-3·46]). Both aspirin (adjusted common OR 0·91 [95% CI 0·69-1·21]) and unfractionated heparin (0·81 [0·61-1·08]) led to a non-significant shift towards worse modified Rankin Scale scores.
Interpretation: Periprocedural intravenous aspirin and unfractionated heparin during endovascular stroke treatment are both associated with an increased risk of symptomatic intracranial haemorrhage without evidence for a beneficial effect on functional outcome. FUNDING: The Collaboration for New Treatments of Acute Stroke consortium, the Brain Foundation Netherlands, the Ministry of Economic Affairs, Stryker, Medtronic, Cerenovus, and the Dutch Heart Foundation.

Gepubliceerd: Lancet. 2022;399(10329):1059-69.
Impact factor: 202.731 ; Q1

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18. Determinants of Symptomatic Intracranial Hemorrhage After Endovascular Stroke Treatment: A Retrospective Cohort Study
van der Steen W, van der Ende NAM, van Kranendonk KR, Chalos V, van Oostenbrugge RJ, van Zwam WH, Roos Y, van Doormaal PJ, van Es A, Lingsma HF, Majoie C, van der Lugt A, Dippel DWJ, Roozenbeek B, MR CLEAN Trial and MR CLEAN Registry Investigators; Brouwers PJAM, Gerrits D.

Background: Symptomatic intracranial hemorrhage (sICH) is a serious complication after endovascular treatment for ischemic stroke. We aimed to identify determinants of its occurrence and location**.**
Methods: We retrospectively analyzed data from the Dutch MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) and MR CLEAN registry. We included adult patients with a large vessel occlusion in the anterior circulation who underwent endovascular treatment within 6.5 hours of stroke onset. We used univariable and multivariable logistic regression analyses to identify determinants of overall sICH occurrence, sICH within infarcted brain tissue, and sICH outside infarcted brain tissue**.**
Results: SICH occurred in 203 (6%) of 3313 included patients and was located within infarcted brain tissue in 50 (25%), outside infarcted brain tissue in 23 (11%), and both within and outside infarcted brain tissue in 116 (57%) patients. In 14 patients (7%), data on location were missing. Prior antiplatelet use, baseline systolic blood pressure, baseline plasma glucose levels, post-endovascular treatment modified treatment in cerebral ischemia score, and duration of procedure were associated with all outcome parameters. In addition, determinants of sICH within infarcted brain tissue included history of myocardial infarction (adjusted odds ratio, 1.65 [95% CI, 1.06-2.56]) and poor collateral score (adjusted odds ratio, 1.42 [95% CI, 1.02-1.95]), whereas determinants of sICH outside infarcted brain tissue included level of occlusion on computed tomography angiography (internal carotid artery or internal carotid artery terminus compared with M1: adjusted odds ratio, 1.79 [95% CI, 1.16-2.78]).
Conclusions: Several factors, some potentially modifiable, are associated with sICH occurrence. Further studies should investigate whether modification of baseline systolic blood pressure or plasma glucose level could reduce the risk of sICH. In addition, determinants differ per location of sICH, supporting the hypothesis of varying underlying mechanisms. REGISTRATION: URL: https://www.isrctn.com/;

Unique identifier: ISRCTN10888758.

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Impact factor: 10.170 ; Q1

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19. Cost Effectiveness of Endovascular Revascularisation vs. Exercise Therapy for Intermittent Claudication Due to Iliac Artery Obstruction
van Reijen NS, van Dieren S, Frans FA, Reekers JA, Metz R, Buscher H, Koelemay MJW, SUPER-study collaborators; Oosterhof-Berktas R.

Objective: To compare cost effectiveness of endovascular revascularisation (ER) and supervised exercise therapy (SET) as primary treatment for patients with intermittent claudication (IC) due to iliac artery obstruction**.**
Methods: Cost utility analysis from a restricted societal perspective and time horizon of 12 months. Patients were included in a multicentre randomised controlled trial (SUPER study, NCT01385774, NTR2648) which compared effectiveness of ER and SET. Health status and health related quality of life (HRQOL) were measured using the Euroqol 5 dimensions 3 levels (EQ5D-3L) and VascuQol-25-NL. Incremental costs were determined per allocated treatment and use of healthcare during follow up. Effectiveness of treatment was determined in quality adjusted life years (QALYs). The difference between treatment groups was calculated by an incremental cost utility ratio (ICER)**.**
Results: Some 240 patients were included, and complete follow up was available for 206 patients (ER 111 , SET 95). The mean costs for patients allocated to ER were €4 031 and €2 179 for SET, a mean difference of €1 852 (95% bias corrected and accelerated [bca] bootstrap confidence interval 1 185 - 2 646). The difference in QALYs during follow up was 0.09 (95% bcaCI 0.04 - 0.13) in favour of ER. The ICER per QALY was €20 805 (95% bcaCI 11 053 - 45 561). The difference in VascuQol sumscore was 0.64 (95% bcaCI 0.39 - 0.91), again in favour of ER**.**
Conclusion: ER as a primary treatment, results in slightly better health outcome and higher QALYs and HRQOL during 12 months of follow up. Although these differences are statistically significant, clinical relevance must be discussed due to the small differences and relatively high cost of ER as primary treatment.

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Impact factor: 6.427 ; Q1

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20. Effect of first pass reperfusion on outcome in patients with posterior circulation ischemic stroke
den Hartog SJ, Roozenbeek B, Boodt N, Bruggeman AAE, van Es A, Emmer BJ, Majoie C, van den Wijngaard IR, van Doormaal PJ, van Zwam WH, Lingsma HF, Dippel DWJ, MR CLEAN Registry investigators; Brouwers PJAM, Gerrits D.

Background: First pass reperfusion (FPR), that is, excellent reperfusion (expanded treatment in cerebral ischemia (eTICI) 2C-3) in one pass, after endovascular treatment (EVT) of an occluded artery in the anterior circulation, is associated with favorable clinical outcome, even when compared with multiple pass excellent reperfusion (MPR). In patients with posterior circulation ischemic stroke (PCS), the same association is expected, but currently unknown. We aimed to assess characteristics associated with FPR and the influence of FPR versus MPR on outcomes in patients with PCS**.**
Methods: We used data from the MR CLEAN Registry, a prospective observational study. The effect of FPR on 24-hour National Institutes of Health Stroke Scale (NIHSS) score, as percentage reduction, and on modified Rankin Scale (mRS) scores at 3 months, was tested with linear and ordinal logistic regression models**.**

Results: Of 224 patients with PCS, 45 patients had FPR, 47 had MPR, and 90 had no excellent reperfusion (eTICI <2C). We did not find an association between any of the patient, imaging, or treatment characteristics and FPR. FPR was associated with better NIHSS (-45% (95% CI: -65% to -12%)) and better mRS scores (adjusted common odds ratio (acOR): 2.16 (95% CI: 1.23 to 3.79)) compared with no FPR. Outcomes after FPR were also more favorable compared with MPR, but the effect was smaller and not statistically significant (NIHSS: -14% (95% CI: -51% to 49%), mRS acOR: 1.50 (95% CI: 0.75 to 3.00)).
Conclusions: FPR in patients with PCS is associated with favorable clinical outcome in comparison with no FPR. In comparison with MPR, the effect of FPR was no longer statistically significant. Nevertheless, our data support the notion that FPR should be the treatment target to pursue in every patient treated with EVT.

Gepubliceerd: J Neurointerv Surg. 2022;14(4):333-40.
Impact factor: 8.572 ; Q1

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21. Editor's Choice - Randomised Clinical Trial of Supervised Exercise Therapy vs. Endovascular Revascularisation for Intermittent Claudication Caused by Iliac Artery Obstruction: The SUPER study
Koelemay MJW, van Reijen NS, van Dieren S, Frans FA, Vermeulen EJG, Buscher HCJL, Reekers JA, SUPER Study Collaborators: Oosterhof-Berktas R, SUPER Study Data Safety Monitoring Committee.

Objective: International guidelines recommend supervised exercise therapy (SET) as primary treatment for all patients with intermittent claudication (IC), yet primary endovascular revascularisation (ER) might be more effective in patients with iliac artery obstruction.
Methods: This was a multicentre RCT including patients with IC caused by iliac artery stenosis or occlusion (NCT01385774). Patients were allocated randomly to SET or ER stratified for maximum walking distance (MWD) and concomitant SFA disease. Primary endpoints were MWD on a treadmill (3.2 km/h, 10% incline) and disease specific quality of life (VascuQol) after one year. Additional interventions during a mean follow up of 5.5 years were recorded.
R**esults**: Between November 2010 and May 2015, 114 patients were allocated to SET, and 126 to ER. The trial was terminated prematurely after 240 patients were included. Compliance with SET was 57/114 (50%) after six months. Ten patients allocated to ER (8%) did not receive this intervention. One year follow up was complete for 90/114 (79%) SET patients and for 104/126 (83%) ER patients. The mean MWD improved from 187 to 561 m in SET patients and from 196 to 574 m in ER patients (p = .69). VascuQol sumscore improved from 4.24 to 5.58 in SET patients, and from 4.28 to 5.88 in ER patients (p = .048). Some 33/114 (29%) SET patients had an ER within one year, and 2/114 (2%) surgical revascularisation (SR). Some 10/126 (8%) ER patients had additional ER within one year and 10/126 (8%) SR. After a mean of 5.5 years, 49% of SET patients and 27% of ER patients underwent an additional intervention for IC.
Conclusion: Taking into account the many limitations of the SUPER study, both a strategy of primary SET and primary ER improve MWD on a treadmill and disease specific Qol of patients with IC caused by an iliac artery obstruction. It seems reasonable to start with SET in these patients and accept a 30% failure rate, which, of course, must be discussed with the patient. Patients continue to have interventions beyond one year.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2022;63(3):421-29.
Impact factor: 6.427 ; Q1

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22. Retrospective evaluation of national MRI reporting quality for lateral lymph nodes in rectal cancer patients and concordance with prospective re-evaluation following additional training
Sluckin TC, Hazen SJA, Horsthuis K, Beets-Tan RGH, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group; Avenarius H, Gielkens H, Hendriksen EM.

Objectives: The presence and size of lateral lymph nodes (LLNs) are important factors influencing treatment decisions for rectal cancer. Awareness of the clinical relevance and describing LLNs in MRI reports is therefore essential. This study assessed whether LLNs were mentioned in primary MRI reports at a national level and investigated the concordance with standardised re-review**.**
Methods: This national, retrospective, cross-sectional cohort study included 1096 patients from 60 hospitals treated in 2016 for primary cT3-4 rectal cancer ≤ 8 cm from the anorectal junction. Abdominal radiologists re-reviewed all MR images following a 2-h training regarding LLNs**.**
Results: Re-review of MR images identified that 41.0% of enlarged (≥ 7 mm) LLNs were not mentioned in primary MRI reports. A contradictory anatomical location was stated for 73.2% of all LLNs and a different size (≥/< 7 mm) for 41.7%. In total, 49.4% of all cases did not mention LLNs in primary MRI reports. Reporting LLNs was associated with stage (cT3N0 44.3%, T3N+/T4 52.8%, $p = 0.013$), cN stage (N0 44.1%, N1 48.6%, N2 59.5%, $p < 0.001$), hospital type (non-teaching 34.6%, teaching 52.2%, academic 53.2% $p = 0.006$) and annual rectal cancer resection volumes (low 34.8%, medium 47.7%, high 57.3% $p < 0.001$). For LLNs present according to original MRI reports (n = 226), 64.2% also mentioned a short-axis size, 52.7% an anatomical location and 25.2% whether it was deemed suspicious.
Conclusions: Almost half of the primary MRI reports for rectal cancer patients treated in the Netherlands in 2016 did not mention LLNs. A significant portion of enlarged LLNs identified during re-review were also not mentioned originally, with considerable discrepancies for location and size. These results imply insufficient awareness and indicate the need for templates, education and training.

Gepubliceerd: Insights Imaging. 2022;13(1):171.
Impact factor: 5.036 ; Q2

Totale impact factor: 342.995
Gemiddelde impact factor: 15.591

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 2.292
Gemiddelde impact factor: 2.292

Radiotherapie

1. ASO Author Reflections: Improvement of Esophageal Cancer Staging by Implementing Mandard Tumor Regression Score
Crull DJ, Hogenes MCH, Hoekstra R, Hendriksen EM, van Det MJ, Kouwenhoven EA.

Gepubliceerd: Ann Surg Oncol. 2022;29(6):3667-8.
Impact factor: 4.339 ; Q1

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2. The Impact of Tumor Regression on Prognosis After Neoadjuvant Chemoradiotherapy in Surgically Treated Esophageal Adenocarcinoma
Crull DJ, Hogenes MCH, Hoekstra R, Hendriksen EM, van Det MJ, Kouwenhoven EA.

Background: The 5-year survival for patients with esophageal carcinoma remains poor despite neoadjuvant therapy and surgery. The eighth American Joint Committee on Cancer (AJCC) staging, based on the neoadjuvant treated TNM (ypTNM) stage of the resection specimen, is used for prognosis. Tumor characteristics such as tumor grade, subtype of adenocarcinoma, and tumor regression scores are not included in this classification. This study aimed to determine the impact of these tumor characteristics on overall survival (OS) and disease-free survival (DFS)**.**
Methods: This retrospective cohort study included 228 patients with esophageal adenocarcinoma. Tumor regression was determined by the Mandard tumor regression (MTR) score. Subtype and grade of adenocarcinoma were confirmed using either the preoperative biopsy or residual tumor tissue after surgery. The MTR was modified to a three-tier classification. The study classified MTR 1 and 2 in one group as a "major response," with MTR 4 and 5 classified in one group as a "minimal response." RESULTS: The median follow-up period was 2.1 years. Combining MTR with AJCC staging did not improve the prognostic value for the prediction of OS. However, the multivariate analysis showed that the prognostic value of AJCC staging for DFS was improved by adding the three-tiered MTR (odds ratio for MTR4+5: 2.46; 95 % confidence interval, 1.07-5.67). Grade or subtype correlated with neither OS nor DFS in the univariate analyses and did not improve the prognostic value of the AJCC staging**.**
Conclusion: Neither adenocarcinoma subtype nor grade influenced OS or DFS. However, the eighth AJCC staging combined with a three-tier MTR provided a better prognostic tool for DFS in esophageal adenocarcinoma treated with esophagectomy after neoadjuvant chemoradiotherapy.

Gepubliceerd: Ann Surg Oncol. 2022;29(6):3658-66.
Impact factor: 4.339 ; Q1

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3. The clinical relevance of various methods of classifying ipsilateral breast tumour recurrence as either true local recurrence or new primary
Jobsen JJ, Struikmans H, Siemerink E, van der Palen J, Heijmans HJ.

Purpose: Describes the relevance of -various classification methods for ipsilateral breast tumour recurrence (IBTR) as either true recurrence (TR) or new primary (NP) on both disease-specific survival (DSS) and distant metastasis-free survival (DMFS).
Method: Two hundred and thirty-four of 4359 women undergoing breast-conserving therapy experienced IBTR. We compared the impact of four known classification methods and two newly created classification methods**.**
Results: For three of the methods, a better DSS was observed for NP compared to TR with the hazard ratio (HR) ranging from 0.5 to 0.6. The new Twente method classification, comprising all classification

criteria of three known methods, and the new Morphology method, using only morphological criteria, had the best HR and confidence interval with a HR 0.5 (95% CI 0.2-1.0) and a HR 0.5 (95% CI 0.3-1.1), respectively. For DMFS, the HR for NP compared to TR ranged from 0.6 to 0.9 for all six methods. The new Morphology method and the Twente method noted the best HR and confidence intervals with a HR 0.6 (95% CI 0.3-1.1) and a HR 0.6 (95% CI 0.4-1.2), respectively**.**
Conclusion: IBTR classified as TR or NP has a prognostic value for both DSS and DMFS, but depends on the classification method used. Developing and validating a generally accepted form of classification are imperative for using TR and NP in clinical practice.

Gepubliceerd: Breast Cancer Res Treat. 2022;195(3):249-62.
Impact factor: 4.624; Q2

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4. Clinical relevance of the timing of radiotherapy after breast-conserving surgery : Results of a large, single-centre, population-based cohort study
Jobsen JJ, Struikmans H, van der Palen J, Siemerink EJM.

Purpose: To investigate the effect of the timing of radiation therapy after breast-conserving surgery in relation to distant metastasis-free survival and disease-specific survival**.**
Methods: The analysis was performed in relation to 4189 women all undergoing breast-conserving therapy (BCT). Three groups were defined with respect to lymph node status and the use of adjuvant systemic therapy (AST). Patients were categorized into time intervals: < 37 days, 37-53 days, 54-112 days and > 112 days**.**
Results: For women without lymph node metastases and with favourable characteristics aged > 55 years, an improved treatment efficacy was noted when starting radiotherapy with a time interval of < 37 days. The same was observed for women with lymph nodes metastases receiving AST aged ≤ 50 years. Finally, for women aged > 50 years with negative lymph node status but with unfavourable characteristics and receiving AST, an improved treatment efficacy was noted when starting radiotherapy after a time interval of ≥ 37 days**.**
Conclusion: The results of our study further support the hypothesis that the timing of radiotherapy may have an impact on treatment efficacy and that further studies (preferably randomized trials) are indicated.

Gepubliceerd: Strahlenther Onkol. 2022;198(3):268-81.
Impact factor: 4.033 ; Q2

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5. Limited Impact of Breast Cancer and Non-breast Malignancies on Survival in Older Patients with Early-Stage Breast Cancer: Results of a Large, Single-Centre, Population-Based Study
Jobsen JJ, van der Palen J, Siemerink E, Struikmans H.

Aims: To analyse the disease-free survival and overall survival in older adults with breast cancer after breast-conserving therapy, focusing on the relevance of non-breast malignancy (NBM) with respect to survival rates.
Material and Methods: Analyses were based on 1205 women aged 65 years and older with breast cancer treated with breast-conserving therapy between 1999 and 2015. Patients were divided into three age categories: 65-70, 71-75 and >75 years. Multivariate survival analysis was carried out using Cox regression analysis**.**
Results: The two youngest age categories showed excellent results, with a 12-year disease-free survival of 84.6 and 86.3%, respectively. We noted a 17.2% incidence of NBM, particularly for colon cancer and lung cancer. Most (72.9%) occurred after a diagnosis of breast cancer. Of those 72.9%,

about 50% died as a result of NBM within 2 years of the diagnosis of NBM. The overall 12-year NBM-specific survival was 92.0%. The 12-year overall survival was 60.0% for all and for the three abovementioned age categories was 73.3, 54.4 and 28.4%, respectively. The cause of death for all was predominantly non-malignancy-related morbidity**.**
Conclusion: The impact of breast cancer on life expectancy was limited, in particularly for women aged 65-75 years. The relevance of NBM on survival was limited.

Gepubliceerd: Clin Oncol (R Coll Radiol). 2022;34(6):355-62.
Impact factor: 4.925; Q2

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6. The association of internal mammary and medial supraclavicular lymph node radiation technique with clinical outcomes: Results from the EORTC 22922/10925 randomised trial
Kaidar-Person O, Fortpied C, Hol S, Weltens C, Kirkove C, Budach V, Peignaux-Casasnovas K, van der Leij F, Vonk E, Valli M, Weidner N, Guckenberger M, Koiter E, Fourquet A, Bartelink H, Struikmans H, Poortmans P.

Background and Purpose: The multicentre EORTC 22922/10925 trial (ClinicalTrials.gov, NCT00002851) was conducted between 1996 and 2004. The trial evaluated the effect of irradiation of the internal mammary and medial supraclavicular lymph node chains (IM-MS) vs no further radiation therapy (RT) on survival and cause of death in breast cancer stage I-III patients. At 15.7 years of median follow-up, a significant reduction of breast cancer specific mortality (BCSM) and any recurrence, not translating in improved overall survival (OS), and low absolute rates of side effects were found. The aim of the current analysis was to evaluate the association of RT techniques of IM-MS lymph node irradiation with long-term outcomes.
Patients and Methods: Three RT techniques were used for IM-MS: a standard technique using a fixed set-up combining photon/electron beams to the IM and tangential fields to the breast or chest wall vs a standard-modified technique with minor adaptation for beam settings vs a more individualised technique based on individual localisation of the IM. Techniques used were fixed per institution over the duration of the trial. We performed an exploratory and descriptive analysis of the outcomes after 15 years follow-up for the three RT techniques**.**
Results: Between July 1996 and January 2004, 46 radiation oncology departments from 13 countries accrued 4004 patients. Median follow-up was 15.7 years. The number of patients treated by each technique was 2440 (61%) by standard vs 635 (16%) by standard-modified vs 929 (23%) patients by individualised technique. The absolute improvements of oncological outcomes in terms of disease-free survival (DFS), OS and BCSM with IM-MS RT compared to no IM-MS RT were 6.8%, 4.9% and -5.8% for the individualised technique, vs 1.6%, 2.9% and -4.3% for modified standard and -1.4%, 1.1% and -3% for standard technique, respectively. The increase in 15-year rates of side effects due to IM-MS RT, both scored longitudinally and cross-sectionally, were similar among the techniques**.**
Conclusion: Even though a straightforward comparison by technique is not possible because of variations in baseline characteristics between institutions, our findings suggest that the use of more individualised RT techniques is associated with higher rates of oncological improvements without increased risks for late side effects.

Gepubliceerd: Radiother Oncol. 2022;172:99-110.
Impact factor: 6.901 ; Q1

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7. Effect of physical exercise on the hippocampus and global grey matter volume in breast cancer patients: A randomized controlled trial (PAM study)

Koevoets EW, Geerlings MI, Monninkhof EM, Mandl R, Witlox L, van der Wall E, Stuiver MM, Sonke GS, Velthuis MJ, Jobsen JJ, van der Palen J, Bos M, Göker E, Menke-Pluijmers MBE, Sommeijer DW, May AM, de Ruiter MB, Schagen SB.

Background: Physical exercise in cancer patients is a promising intervention to improve cognition and increase brain volume, including hippocampal volume. We investigated whether a 6-month exercise intervention primarily impacts total hippocampal volume and additionally hippocampal subfield volumes, cortical thickness and grey matter volume in previously physically inactive breast cancer patients. Furthermore, we evaluated associations with verbal memory**.**
Methods: Chemotherapy-exposed breast cancer patients (stage I-III, 2-4 years post diagnosis) with cognitive problems were included and randomized in an exercise intervention (n = 70, age = 52.5 ± 9.0 years) or control group (n = 72, age = 53.2 ± 8.6 years). The intervention consisted of 2x1 hours/week of supervised aerobic and strength training and 2x1 hours/week Nordic or power walking. At baseline and at 6-month follow-up, volumetric brain measures were derived from 3D T1-weighted 3T magnetic resonance imaging scans, including hippocampal (subfield) volume (FreeSurfer), cortical thickness (CAT12), and grey matter volume (voxel-based morphometry CAT12). Physical fitness was measured with a cardiopulmonary exercise test. Memory functioning was measured with the Hopkins Verbal Learning Test-Revised (HVLT-R total recall) and Wordlist Learning of an online cognitive test battery, the Amsterdam Cognition Scan (ACS Wordlist Learning). An explorative analysis was conducted in highly fatigued patients (score of ≥ 39 on the symptom scale 'fatigue' of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire), as previous research in this dataset has shown that the intervention improved cognition only in these patients**.**
Results: Multiple regression analyses and voxel-based morphometry revealed no significant intervention effects on brain volume, although at baseline increased physical fitness was significantly related to larger brain volume (e.g., total hippocampal volume: R = 0.32, B = 21.7 mm(3), 95 % CI = 3.0 - 40.4). Subgroup analyses showed an intervention effect in highly fatigued patients. Unexpectedly, these patients had significant reductions in hippocampal volume, compared to the control group (e.g., total hippocampal volume: B = -52.3 mm(3), 95 % CI = -100.3 - -4.4)), which was related to improved memory functioning (HVLT-R total recall: B = -0.022, 95 % CI = -0.039 - -0.005; ACS Wordlist Learning: B = -0.039, 95 % CI = -0.062 - -0.015).
Conclusions: No exercise intervention effects were found on hippocampal volume, hippocampal subfield volumes, cortical thickness or grey matter volume for the entire intervention group. Contrary to what we expected, in highly fatigued patients a reduction in hippocampal volume was found after the intervention, which was related to improved memory functioning. These results suggest that physical fitness may benefit cognition in specific groups and stress the importance of further research into the biological basis of this finding.

Gepubliceerd: Neuroimage Clin. 2022;37:103292.
Impact factor: 4.891 ; Q2

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8. Effect of physical exercise on cognitive function after chemotherapy in patients with breast cancer: a randomized controlled trial (PAM study)
Koevoets EW, Schagen SB, de Ruiter MB, Geerlings MI, Witlox L, van der Wall E, Stuiver MM, Sonke GS, Velthuis MJ, Jobsen JJ, Menke-Pluijmers MBE, Göker E, van der Pol CC, Bos M, Tick LW, van Holsteijn NA, van der Palen J, May AM, Monninkhof EM.

Background: Up to 60% of breast cancer patients treated with chemotherapy is confronted with cognitive problems, which can have a significant impact on daily activities and quality of life (QoL).

We investigated whether exercise training improves cognition in chemotherapy-exposed breast cancer patients 2-4 years after diagnosis**.**
Methods: Chemotherapy-exposed breast cancer patients, with both self-reported cognitive problems and lower than expected performance on neuropsychological tests, were randomized to an exercise or control group. The 6-month exercise intervention consisted of supervised aerobic and strength training (2 h/week), and Nordic/power walking (2 h/week). Our primary outcome was memory functioning (Hopkins Verbal Learning Test-Revised; HVLT-R). Secondary outcomes included online neuropsychological tests (Amsterdam Cognition Scan; ACS), self-reported cognition (MD Anderson Symptom Inventory for multiple myeloma; MDASI-MM), physical fitness (relative maximum oxygen uptake; VO(2peak)), fatigue (Multidimensional Fatigue Inventory), QoL (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ C-30), depression (Patient Health Questionnaire-9, Hospital Anxiety and Depression Scale; HADS), and anxiety (HADS). HVLT-R total recall was analyzed with a Fisher exact test for clinically relevant improvement (≥ 5 words). Other outcomes were analyzed using multiple regression analyses adjusted for baseline and stratification factors**.**
Results: We randomized 181 patients to the exercise (n = 91) or control group (n = 90). Two-third of the patients attended ≥ 80% of the exercise sessions, and physical fitness significantly improved compared to control patients (B VO(2peak) 1.4 ml/min/kg, 95%CI:0.6;2.2). No difference in favor of the intervention group was seen on the primary outcome. Significant beneficial intervention effects were found for self-reported cognitive functioning [MDASI-MM severity (B-0.7, 95% CI - 1.2; - 0.1)], fatigue, QoL, and depression. A hypothesis-driven analysis in highly fatigued patients showed positive exercise effects on tested cognitive functioning [ACS Reaction Time (B-26.8, 95% CI - 52.9; - 0.6) and ACS Wordlist Learning (B4.4, 95% CI 0.5; 8.3)].
Conclusions: A 6-month exercise intervention improved self-reported cognitive functioning, physical fitness, fatigue, QoL, and depression in chemotherapy-exposed breast cancer patients with cognitive problems. Tested cognitive functioning was not affected. However, subgroup analysis indicated a positive effect of exercise on tested cognitive functioning in highly fatigued patients. Trial Registration Netherlands Trial Registry: Trial NL5924 (NTR6104). Registered 24 October 2016, https://www.trialregister.nl/trial/5924 .

Gepubliceerd: Breast Cancer Res. 2022;24(1):36.
Impact factor: 8.408; Q1

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9. Defining Substantial Lymphovascular Space Invasion in Endometrial Cancer
Peters EEM, León-Castillo A, Smit V, Boennelycke M, Hogdall E, Hogdall C, Creutzberg C, Jürgenliemk-Schulz IM, Jobsen JJ, Mens JWM, Lutgens L, van der Steen-Banasik EM, Ortoft G, Bosse T, Nout R.

Lymphovascular space invasion (LVSI) occurs in a minority of endometrial cancer (EC) cases, and the extent of LVSI is an important risk factor for recurrence and/or metastases. Our aim was to improve the reproducibility of measuring clinically meaningful LVSI by performing a quantitative analysis of the correlation between LVSI and the risk of pelvic lymph node recurrence in EC. EC samples from PORTEC-1 and PORTEC-2 trials were retrieved and used to collect quantitative data, including the number of LVSI-positive vessels per H&E-stained slide. Using a predefined threshold for clinical relevance, the risk of pelvic lymph node recurrence risk was calculated (Kaplan-Meier method, with Cox regression) using a stepwise adjustment for the number of LVSI-positive vessels. This analysis was then repeated in the Danish Gynecological Cancer Database (DGCD) cohort. Among patients in PORTEC-1 and PORTEC-2 trials who did not receive external beam radiotherapy, the 5-yr pelvic lymph node recurrence risk was 3.3%, 6.7% (P=0.51), and 26.3% (P<0.001), respectively when 0, 1 to 3, or ≥4 vessels had LVSI involvement; similar results were obtained for the DGCD cohort. Furthermore, both the average number of tumor cells in the largest embolus and the number of LVSI-positive H&E

slides differed significantly between focal LVSI and substantial LVSI. On the basis of these results, we propose a numeric threshold (≥4 LVSI-involved vessels in at least one H&E slide) for defining clinically relevant LVSI in EC, thereby adding supportive data to the semiquantitative approach. This will help guide gynecologic pathologists to differentiate between focal and substantial LVSI, especially in borderline cases.

Gepubliceerd: Int J Gynecol Pathol. 2022;41(3):220-6.
Impact factor: 3.326 ; Q2

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10. Retrospective evaluation of national MRI reporting quality for lateral lymph nodes in rectal cancer patients and concordance with prospective re-evaluation following additional training
Sluckin TC, Hazen SJA, Horsthuis K, Beets-Tan RGH, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group; Avenarius H, Gielkens H, Hendriksen EM.

Objectives: The presence and size of lateral lymph nodes (LLNs) are important factors influencing treatment decisions for rectal cancer. Awareness of the clinical relevance and describing LLNs in MRI reports is therefore essential. This study assessed whether LLNs were mentioned in primary MRI reports at a national level and investigated the concordance with standardised re-review**.**
Methods: This national, retrospective, cross-sectional cohort study included 1096 patients from 60 hospitals treated in 2016 for primary cT3-4 rectal cancer ≤ 8 cm from the anorectal junction. Abdominal radiologists re-reviewed all MR images following a 2-h training regarding LLNs**.**
Results: Re-review of MR images identified that 41.0% of enlarged (≥ 7 mm) LLNs were not mentioned in primary MRI reports. A contradictory anatomical location was stated for 73.2% of all LLNs and a different size (≥/< 7 mm) for 41.7%. In total, 49.4% of all cases did not mention LLNs in primary MRI reports. Reporting LLNs was associated with stage (cT3N0 44.3%, T3N+/T4 52.8%, $p = 0.013$), cN stage (N0 44.1%, N1 48.6%, N2 59.5%, $p < 0.001$), hospital type (non-teaching 34.6%, teaching 52.2%, academic 53.2% $p = 0.006$) and annual rectal cancer resection volumes (low 34.8%, medium 47.7%, high 57.3% $p < 0.001$). For LLNs present according to original MRI reports (n = 226), 64.2% also mentioned a short-axis size, 52.7% an anatomical location and 25.2% whether it was deemed suspicious.
Conclusions: Almost half of the primary MRI reports for rectal cancer patients treated in the Netherlands in 2016 did not mention LLNs. A significant portion of enlarged LLNs identified during re-review were also not mentioned originally, with considerable discrepancies for location and size. These results imply insufficient awareness and indicate the need for templates, education and training.

Gepubliceerd: Insights Imaging. 2022;13(1):171.
Impact factor: 5.036 ; Q2

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11. Microcystic elongated and fragmented (MELF) pattern of invasion: Molecular features and prognostic significance in the PORTEC-1 and -2 trials
van den Heerik A, Aiyer KTS, Stelloo E, Jürgenliemk-Schulz IM, Lutgens L, Jobsen JJ, Mens JWM, van der Steen-Banasik EM, Creutzberg CL, Smit V, Horeweg N, Bosse T.

Objective: Microcystic, elongated fragmented (MELF) pattern of myometrial invasion is a distinct histologic feature occasionally seen in low-grade endometrial carcinomas (EC). The prognostic relevance of MELF invasion was uncertain due to conflicting data, and it had not yet appropriately been studied in the context of the molecular EC classification. We aimed to determine the relation of

MELF invasion with clinicopathological and molecular characteristics, and define its prognostic relevance in early-stage low/intermediate risk EC**.**
Methods: Single whole tumor slides of 979 (85.8%) out of 1141 (high)intermediate-risk EC of women who participated in the PORTEC-1/-2 trials were available for review. Clinicopathological and molecular features were compared between MELF invasion positive and negative cases. Time-to-event analyses were done by Kaplan-Meier method, log-rank tests and Cox' proportional hazards models**.**
Results: MELF invasion was found in 128 (13.1%) cases, and associated with grade 1-2 histology, deep myometrial invasion and substantial lymph-vascular space invasion (LVSI). 85.6% of MELF invasion positive tumors were no-specific-molecular-profile (NSMP) EC. NSMP EC with MELF invasion were CTNNB1 wild type in 92.2% and KRAS mutated in 24.4% of cases. Risk of recurrence was lower for MELF invasion positive as compared to MELF invasion negative cases (4.9% vs. 12.7%, p = 0.026). However, MELF invasion had no independent impact on risk of recurrence (HR 0.65, p = 0.30) after correction for clinicopathological and molecular factors.
Conclusions: MELF invasion has no independent impact on risk of recurrence in early-stage EC, and is frequently observed in low-grade NSMP tumors. Routine assessment of MELF invasion has no clinical implications and is not recommended.

Gepubliceerd: Gynecol Oncol. 2022;166(3):530-7.
Impact factor: 5.304 ; Q1

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12. Comparing costs of standard Breast-Conserving Surgery to Oncoplastic Breast-Conserving Surgery and Mastectomy with Immediate two-stage Implant-Based Breast Reconstruction
Witmer TJK, Kouwenberg CAE, Bargon CA, de Leeuw DM, Koiter E, Siemerink EJM, Mureau MAM, Rakhorst HA.

Background: Conventional breast-conserving surgery (C-BCS) has equal oncological outcomes and superior cosmetic and patient-reported outcomes compared to mastectomy with immediate two-stage implant-based breast reconstruction (M-IBR). Oncoplastic breast-conserving surgery (OP-BCS) is increasingly being used, as it often has better cosmetic results and it enables larger tumour resection. However, OP-BCS and M-IBR compared to C-BCS lengthens operative time and might lead to more complications and consequently to additional costs. Therefore, this study aimed to compare costs and complication rates of C-BCS, OP-BCS and M-IBR**.**
Methods: This single-centre, retrospective cohort study, calculated costs for all patients who had undergone breast cancer surgery between January 2014 and December 2016. Patient-, tumour- and surgery-related data of C-BCS, OP-BCS and M-IBR patients were retrieved by medical record review. Treatment costs were calculated using hospital financial data. Differences in costs and complications were analysed**.**
Results: A total of 220 patients were included: 74 patients in the C-BCS, 78 in the OP-BCS and 68 in the M-IBR group. From most expensive to least expensive, differences in total costs were found between C-BCS vs. OP-BCS and C-BCS vs. M-IBR (p=<0.01 and p=0.04, respectively). Costs of OP-BCS and M-IBR were comparable. Complication rates were 5.5% for C-BCS, followed by 17% for OP-BCS, and 34% for M-IBR (p<0.01)**.**
Conclusion: Considering total treatment costs, OP-BCS was financially non-inferior to M-IBR, whereas complication rates were higher following M-IBR. Therefore, when considering other benefits of OP-BCS, such as higher patient-reported outcomes and similar oncological outcomes, a shift from M-IBR to BCS using oncoplastic techniques seems justified.

Gepubliceerd: J Plast Reconstr Aesthet Surg. 2022;75(8):2569-76.
Impact factor: 3.022 ; Q2

13. Cone-beam computed tomography-guided online adaptive radiotherapy is feasible for prostate cancer patients
Zwart LGM, Ong F, Ten Asbroek LA, van Dieren EB, Koch SA, Bhawanie A, de Wit E, Dasselaar JJ.

Background and Purpose: Studies have shown the potential of cone-beam computed tomography (CBCT)-guided online adaptive radiotherapy (oART) for prostate cancer patients in a simulation environment. The aim of this study was to evaluate the feasibility of the clinical implementation of CBCT-guided oART for prostate cancer patients.
Material and Methods: Between February and July 2020, eleven prostate cancer patients were treated with CBCT-guided oART using a fractionation scheme of 20 × 3 Gy to the prostate and 20 × 2.7/3.0 Gy to the seminal vesicles for more advanced stages. The on-couch adaptive workflow consisted of influencer (prostate, seminal vesicles, rectum, bladder) review, target review, scheduled (re-calculated) and adapted (re-optimized) plan generation, an independent QA procedure and treatment delivery. Treatment time, proportion of adapted fractions and reasons for plan adaptation were evaluated**.**
Results: Mean total treatment time (±SD) from CBCT acquisition to end of treatment delivery was 17.5 ± 3.2 min (range: 10.8-28.8 min). In all 220 fractions, the PTV coverage was increased for the adapted plan compared to the scheduled plan. The V60Gy of bladder and rectum were below the constraints (<5% and <3%) for both scheduled and adapted plans in 171 out of 220 fractions and for the adapted plan only in 30 out of 220 fractions. In 19 out of 220 fractions, the V60Gy of the bladder and/or rectum was above the constraint for the adapted plan.
Conclusions: The clinical implementation of CBCT-guided oART is feasible for prostate cancer patients. The adaptive workflow is possible within twenty minutes on average with a dedicated team.

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Impact factor: 3.700 ; Q NVT

Totale impact factor: 62.949
Gemiddelde impact factor: 4.834

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 17.282
Gemiddelde impact factor: 4.321

Reumatologie

1. Exploring discordance between Health Literacy Questionnaire scores of people with RMDs and assessment by treating health professionals
Bakker MM, Putrik P, Dikovec C, Rademakers J, Vonkeman HE, Kok MR, Voorneveld-Nieuwenhuis H, Ramiro S, de Wit M, Buchbinder R, Batterham R, Osborne RH, Boonen A.

Objectives: We studied discordance between health literacy of people with rheumatic and musculoskeletal diseases (RMDs) and assessment of health literacy by their treating health professionals, and explored whether discordance is associated with the patients' socioeconomic background**.**
Methods: Patients with RA, spondyloarthritis (SpA) or gout from three Dutch outpatient rheumatology clinics completed the nine-domain Health Literacy Questionnaire (HLQ). Treating health professionals assessed their patients on each HLQ domain. Discordance per domain was defined as a ≥2-point difference on a 0-10 scale (except if both scores were below three or above seven), leading to three categories: 'negative discordance' (i.e. professional scored lower), 'probably the same' or 'positive discordance' (i.e. professional scored higher). We used multivariable multilevel multinomial regression models with patients clustered by health professionals to test associations with socioeconomic factors (age, gender, education level, migration background, employment, disability for work, living alone)**.**
Results: We observed considerable discordance (21-40% of patients) across HLQ domains. Most discordance occurred for 'Critically appraising information' (40.5%, domain 5). Comparatively, positive discordance occurred more frequently. Negative discordance was more frequently and strongly associated with socioeconomic factors, specifically lower education level and non-Western migration background (for five HLQ domains). Associations between socioeconomic factors and positive discordance were less consistent**.**
Conclusion: Frequent discordance between patients' scores and professionals' estimations indicates there may be hidden challenges in communication and care, which differ between socioeconomic groups. Successfully addressing patients' health literacy needs cannot solely depend on health professionals' estimations but will require measurement and dialogue. VIDEO ABSTRACT: A video abstract of this article can be found at https://www.youtube.com/watch?v=ggnB1rATdQ4.

Gepubliceerd: Rheumatology (Oxford). 2022;62(1):52-64.
Impact factor: 7.046 ; Q1

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2. Performance of 3 Composite Measures for Disease Activity in Peripheral Spondyloarthritis
Beckers E, Been M, Webers C, Boonen A, Ten Klooster PM, Vonkeman HE, van Tubergen A.

Objective: To investigate concurrent validity and discrimination of the Disease Activity Index for Psoriatic Arthritis (DAPSA) score, Psoriatic Arthritis Disease Activity Score (PASDAS), and Ankylosing Spondylitis Disease Activity Score (ASDAS) in peripheral spondyloarthritis (pSpA) in clinical practice**.**
Methods: Data from a Dutch registry for SpA (SpA-Net) were used. Predefined hypotheses on concurrent validity of the composite measures with 15 other outcome measures of disease activity, physical function, and health-related quality of life were tested. Concurrent validity was considered acceptable if ≥ 75% of the hypotheses were confirmed. Discrimination was assessed by stratifying patients in DAPSA, PASDAS, and ASDAS predefined disease activity states and studying mean differences in health outcomes by 1-way ANOVA. Further, the concordance in disease activity states was determined. All analyses were repeated in subgroups with and without psoriasis (PsO)**.**
Results: DAPSA, PASDAS, and ASDAS scores were available for 191, 139, and 279 patients with pSpA, respectively. The concurrent validity and discrimination of all composite measures were acceptable,

as the strength of correlations were as hypothesized in ≥ 75% of the studied correlations. With increasing disease activity states, scores in nearly all outcome measures worsened significantly. The DAPSA, PASDAS, and ASDAS classified 22%, 56%, and 48% of the patients, respectively, in the 2 highest disease activity states. Stratified analyses for concomitant PsO revealed no relevant subgroup differences**.**
Conclusion: The performance of DAPSA, PASDAS, and ASDAS in pSpA was acceptable, and independent of concomitant PsO. Due to discrepancy in classification, the validity of existing thresholds for disease activity states warrants further study in pSpA.

Gepubliceerd: J Rheumatol. 2022;49(3):256-64.
Impact factor: 5.346 ; Q2

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3. Treat-to-target in axial spondyloarthritis: an observational study in daily practice
Beckers E, Boonen A, Webers C, Ten Klooster P, Vonkeman H, Efdé M, van Tubergen A.

Objectives: To evaluate the extent to which internationally agreed treat-to-target recommendations were applied in clinical practice in patients with axial spondyloarthritis**.**
Methods: Data were used from a web-based patient registry for monitoring SpA in daily practice in the Netherlands. The extent to which treat-to-target was applied was evaluated through four indicators: the proportion of patients (i) with ≥1 Ankylosing Spondylitis Disease Activity Score (ASDAS) assessed during a 1-year period, (ii) having inactive disease/low disease activity (i.e. ASDAS < 2.1), (iii) in whom re-evaluation of ASDAS within recommended intervals occurred, and (iv) with high disease activity (HDA, i.e. ASDAS ≥ 2.1) in whom treatment was adapted ≤6 weeks after obtaining ASDAS ≥ 2.1. Patients with HDA with treatment adaptations were compared with patients with HDA without treatment adaptations**.**
Results: In 185 out of 219 patients (84%), disease activity was monitored with ≥1 ASDAS during a 1-year period, of whom 71 (38%) patients had a score below the target (ASDAS < 2.1) at first measurement. Re-evaluation of ASDAS ≤3 months occurred in 11% and 23% of the patients with inactive disease/low disease activity and HDA, respectively. Treatment adaptation occurred in 19 out of 114 patients (17%) with HDA. Patients in whom treatment was adapted had significantly higher ASDAS ($P < 0.01$), CRP levels ($P < 0.05$) and physician global assessment ($P < 0.05$) compared with patients without treatment adaptations.
Conclusions: Treat-to-target was applied to a limited extent in clinical practice in patients with axial spondyloarthritis. Available disease activity scores seemed not to be used for determining the frequency of re-evaluation nor treatment adaptation.

Gepubliceerd: Rheumatology (Oxford). 2022;61(4):1396-407.
Impact factor: 7.046 ; Q1

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4. Continuous effectiveness and safety after a hospital-wide switch to adalimumab biosimilar: An observational study in rheumatoid arthritis patients
Brouwer R, Ten Klooster PM, Masselink JB, Vonkeman HE.

The objective of this study was to examine the maintenance of effect and safety after a hospital-wide switch for economic reasons from adalimumab originator Humira® to biosimilar Amgevita® in real-world rheumatoid arthritis (RA) patients and patient satisfaction with the switch. We conducted a single-center retrospective observational study of RA patients on the course of their disease activity (DAS28, ESR, and CRP), health-related quality of life (SF-36), and functional disability (HAQ-DI) before and up to 1 year after the switch, supplemented with a cross-sectional survey on satisfaction and

experienced side effects approximately 18 months after the switch. Treatment outcomes were analyzed with linear mixed modeling and generalized estimating equations. Of 52 RA patients sufficient data were available. Disease activity levels, the proportion of patients in remission, and SF-36 and HAQ-DI scores did not significantly change from before the switch. Overall, patients were satisfied with the switch. Three patients (7.9%) stopped the biosimilar due to side effects. In conclusion, switching to the adalimumab biosimilar did not result in increased disease activity or worse patient-reported outcomes. Also, there was no apparent evidence of increased side effects. Patients themselves were mostly satisfied with the switching experience.

Gepubliceerd: Pharmacol Res Perspect. 2022;10(6):e01025.
Impact factor: 2.963 ; Q3

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5. ISARIC-COVID-19 dataset: A Prospective, Standardized, Global Dataset of Patients Hospitalized with COVID-19
Garcia-Gallo E, Merson L, Kennon K, Kelly S, Citarella BW, Fryer DV, Shrapnel S, Lee J, Duque S, Fuentes YV, Balan V, Smith S, Wei J, Gonçalves BP, Russell CD, Sigfrid L, Dagens A, Olliaro PL, Baruch J, Kartsonaki C, Dunning J, Rojek A, Rashan A, Beane A, Murthy S, Reyes LF, ISARIC Clinical Characterization Group: Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H.

The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) COVID-19 dataset is one of the largest international databases of prospectively collected clinical data on people hospitalized with COVID-19. This dataset was compiled during the COVID-19 pandemic by a network of hospitals that collect data using the ISARIC-World Health Organization Clinical Characterization Protocol and data tools. The database includes data from more than 705,000 patients, collected in more than 60 countries and 1,500 centres worldwide. Patient data are available from acute hospital admissions with COVID-19 and outpatient follow-ups. The data include signs and symptoms, pre-existing comorbidities, vital signs, chronic and acute treatments, complications, dates of hospitalization and discharge, mortality, viral strains, vaccination status, and other data. Here, we present the dataset characteristics, explain its architecture and how to gain access, and provide tools to facilitate its use.

Gepubliceerd: Sci Data. 2022;9(1):454.
Impact factor: 8.501 ; Q1

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6. Barriers and facilitators for systematically registering adverse drug reactions in electronic health records: a qualitative study with Dutch healthcare professionals
Geeven I, Jessurun NT, Wasylewicz ATM, Drent M, Spuls PI, Hoentjen F, van Puijenbroek EP, Vonkeman HE, Grootens KP, van Doorn MBA, van Den Bemt BJF, Bekker CL.

Background: Systematically registering ADRs in electronic health records (EHRs) likely contribute to patient safety as it enables the exchange of drug safety data. Currently, ADRs registrations by healthcare professionals (HCPs) is suboptimal. This study aimed to identify barriers and facilitators perceived by HCPs to register ADRs systematically in EHRs.
Research design and methods: A qualitative study with individual interviews was conducted among specialist physicians and hospital pharmacists from 10 different Dutch hospitals. A semi-structured interview guide was used to identify experienced barriers and facilitators for systematically registering ADRs. Data was analyzed following thematic analysis. Themes within barriers and facilitators were aligned with the Capability-Opportunity-Motivation-Behavior (COM-B) framework**.**

Results: In total, 16 HCPs were interviewed. Identified barriers were: lack of knowledge to recognize ADRs, time constraints, inadequate IT system, lack of support, stuck in routine, and not recognizing the importance of registering ADRs. Identified facilitators were: enhanced knowledge and awareness of ADRs, functional IT systems, expanding accountability for registration, and motivation toward registering.
Conclusions: Barriers and facilitators for registering spanned all aspects of the COM-B model and occurred in individual, social and environmental domains. Addressing these aspects could improve the registration of ADRs and may contribute to patient safety.

Gepubliceerd: Expert Opin Drug Saf. 2022;21(5):699-706.
Impact factor: 4.011 ; Q2

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7. Clinical presentation, disease course, and outcome of COVID-19 in hospitalized patients with and without pre-existing cardiac disease: a cohort study across 18 countries
CAPACITY-COVID Collaborative Consortium and LEOSS Study Group; Delsing CE, Meijs MFL, van Veen H, Vonkeman HE.

Aims: Patients with cardiac disease are considered high risk for poor outcomes following hospitalization with COVID-19. The primary aim of this study was to evaluate heterogeneity in associations between various heart disease subtypes and in-hospital mortality**.**
Methods and Results: We used data from the CAPACITY-COVID registry and LEOSS study. Multivariable Poisson regression models were fitted to assess the association between different types of pre-existing heart disease and in-hospital mortality. A total of 16 511 patients with COVID-19 were included (21.1% aged 66-75 years; 40.2% female) and 31.5% had a history of heart disease. Patients with heart disease were older, predominantly male, and often had other comorbid conditions when compared with those without. Mortality was higher in patients with cardiac disease (29.7%; n = 1545 vs. 15.9%; n = 1797). However, following multivariable adjustment, this difference was not significant [adjusted risk ratio (aRR) 1.08, 95% confidence interval (CI) 1.02-1.15; P = 0.12 (corrected for multiple testing)]. Associations with in-hospital mortality by heart disease subtypes differed considerably, with the strongest association for heart failure (aRR 1.19, 95% CI 1.10-1.30; P < 0.018) particularly for severe (New York Heart Association class III/IV) heart failure (aRR 1.41, 95% CI 1.20-1.64; P < 0.018). None of the other heart disease subtypes, including ischaemic heart disease, remained significant after multivariable adjustment. Serious cardiac complications were diagnosed in <1% of patients**.**
Conclusion: Considerable heterogeneity exists in the strength of association between heart disease subtypes and in-hospital mortality. Of all patients with heart disease, those with heart failure are at greatest risk of death when hospitalized with COVID-19. Serious cardiac complications are rare during hospitalization.

Gepubliceerd: Eur Heart J. 2022;43(11):1104-20.
Impact factor: 35.855 ; Q1

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8. Intravenous pegylated liposomal prednisolone outperforms intramuscular methylprednisolone in treating rheumatoid arthritis flares: A randomized controlled clinical trial
Metselaar JM, Middelink LM, Wortel CH, Bos R, van Laar JM, Vonkeman HE, Westhovens R, Lammers T, Yao SL, Kothekar M, Raut A, Bijlsma JWJ.

Glucocorticoids (GCs) are potent anti-inflammatory drugs but their use is limited by systemic exposure leading to toxicity. Targeted GC delivery to sites of inflammation via encapsulation in long-

circulating liposomes may improve the therapeutic index. We performed a randomized, double-blind, active-controlled, multi-center study in which intravenously (i.v.) administered pegylated liposomal prednisolone sodium phosphate (Nanocort) was compared to equipotent intramuscular (i.m.) methylprednisolone acetate (Depo-Medrol®; i.e. a current standards-of-care for treating flares in rheumatoid arthritis patients). We enrolled 172 patients with active arthritis who met all eligibility criteria, eventually resulting in 150 patients randomized in three groups: (1) Nanocort 75 mg i.v. infusion plus i.m. saline injection; (2) Nanocort 150 mg i.v. infusion plus i.m. saline injection; and (3) Depo-Medrol® 120 mg i.m. injection plus i.v. saline infusion. Dosing in each group occurred at baseline and on day 15 (week 2). Study visits occurred at week 1, 2, 3, 4, 6, 8 and 12, to assess both efficacy and safety. The primary endpoint was the "European League Against Rheumatism" (EULAR) responder rate at week 1. Safety was determined by the occurrence of adverse events during treatment and 12 weeks of follow-up. Treatment with Nanocort was found to be superior to Depo-Medrol® in terms of EULAR response at week 1, with p-values of 0.007 (good response) and 0.018 (moderate response). Treatments were well tolerated with a comparable pattern of adverse events in the three treatment groups. However, the Nanocort groups had a higher incidence of hypersensitivity reactions during liposome infusion. Our results show that liposomal Nanocort is more effective than Depo-Medrol® in treating patients with rheumatoid arthritis flares and has similar safety. This is the first clinical study in a large patient population showing that i.v. administered targeted drug delivery with a nanomedicine formulation improves the therapeutic index of glucocorticoids.

Gepubliceerd: J Control Release. 2022;341:548-54.
Impact factor: 11.467 ; Q1

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9. Gaming for Adherence to Medication using Ehealth in Rheumatoid arthritis (GAMER) study: a randomised controlled trial

Pouls BPH, Bekker CL, Gundogan F, Hebing RC, van Onzenoort HA, van de Ven LI, Vonkeman HE, Tieben R, Vriezekolk JE, van Dulmen S, Van den Bemt B.

Objective: To examine the effect on adherence to disease modifying anti-rheumatic drugs (DMARDs) in participants with rheumatoid arthritis (RA) of a serious game that targeted implicit attitudes toward medication**.**
Methods: A multicentre randomised controlled trial (RCT) was performed with adults with RA that used DMARDs and possessed a smartphone/tablet. Control and intervention groups received care as usual. The intervention group played the serious game at will during 3 months. Game play data and online questionnaires Compliance Questionnaire on Rheumatology (CQR), Beliefs about Medicine Questionnaire (BMQ), Health Assessment Questionnaire (HAQ) and Rheumatoid Arthritis Disease Activity Index (RADAI) were collected. Primary outcome was DMARD implementation adherence operationalised as the difference in proportion of non-adherent participants (<80% taking adherence) between intervention and control group after 3 months using a Chi-squared test. Two sample t-tests and Wilcoxon rank-sum test were performed to test for differences on secondary outcomes**.**
Results: Of the 110 intervention participants that started the study, 87 participants (79%) installed the game and had a median playtime of 9.7 hours at 3 months. Overall, 186 participants completed the study. Adherence in intervention group (63%) and control group (54%) did not differ significantly (p=0.13) at 3 months. Neither were there differences oberved in CQR continuous score, beliefs about medication (BMQ) or clinical outcomes (HAQ and RADAI)**.**
Conclusion: A serious game aimed at reinterpreting attitudes toward medication failed to show an effect on adherence to DMARDs or clinical outcomes in patients with RA. The game was played frequently indicating that it can be an effective channel for reaching patients.

Trial registration number: NL7217.

Gepubliceerd: RMD Open. 2022;8(2).
Impact factor: 5.806 ; Q1

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10. Respiratory support in patients with severe COVID-19 in the International Severe Acute Respiratory and Emerging Infection (ISARIC) COVID-19 study: a prospective, multinational, observational study

Reyes LF, Murthy S, Garcia-Gallo E, Merson L, Ibáñez-Prada ED, Rello J, Fuentes YV, Martin-Loeches I, Bozza F, Duque S, Taccone FS, Fowler RA, Kartsonaki C, Gonçalves BP, Citarella BW, Aryal D, Burhan E, Cummings MJ, Delmas C, Diaz R, Figueiredo-Mello C, Hashmi M, Panda PK, Jiménez MP, Rincon DFB, Thomson D, Nichol A, Marshall JC, Olliaro PL, ISARIC Characterization Group: Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H.

Background: Up to 30% of hospitalised patients with COVID-19 require advanced respiratory support, including high-flow nasal cannulas (HFNC), non-invasive mechanical ventilation (NIV), or invasive mechanical ventilation (IMV). We aimed to describe the clinical characteristics, outcomes and risk factors for failing non-invasive respiratory support in patients treated with severe COVID-19 during the first two years of the pandemic in high-income countries (HICs) and low middle-income countries (LMICs)**.**
Methods: This is a multinational, multicentre, prospective cohort study embedded in the ISARIC-WHO COVID-19 Clinical Characterisation Protocol. Patients with laboratory-confirmed SARS-CoV-2 infection who required hospital admission were recruited prospectively. Patients treated with HFNC, NIV, or IMV within the first 24 h of hospital admission were included in this study. Descriptive statistics, random forest, and logistic regression analyses were used to describe clinical characteristics and compare clinical outcomes among patients treated with the different types of advanced respiratory support**.**
Results: A total of 66,565 patients were included in this study. Overall, 82.6% of patients were treated in HIC, and 40.6% were admitted to the hospital during the first pandemic wave. During the first 24 h after hospital admission, patients in HICs were more frequently treated with HFNC (48.0%), followed by NIV (38.6%) and IMV (13.4%). In contrast, patients admitted in lower- and middle-income countries (LMICs) were less frequently treated with HFNC (16.1%) and the majority received IMV (59.1%). The failure rate of non-invasive respiratory support (i.e. HFNC or NIV) was 15.5%, of which 71.2% were from HIC and 28.8% from LMIC. The variables most strongly associated with non-invasive ventilation failure, defined as progression to IMV, were high leukocyte counts at hospital admission (OR [95%CI]; 5.86 [4.83-7.10]), treatment in an LMIC (OR [95%CI]; 2.04 [1.97-2.11]), and tachypnoea at hospital admission (OR [95%CI]; 1.16 [1.14-1.18]). Patients who failed HFNC/NIV had a higher 28-day fatality ratio (OR [95%CI]; 1.27 [1.25-1.30]).
Conclusions: In the present international cohort, the most frequently used advanced respiratory support was the HFNC. However, IMV was used more often in LMIC. Higher leucocyte count, tachypnoea, and treatment in LMIC were risk factors for HFNC/NIV failure. HFNC/NIV failure was related to worse clinical outcomes, such as 28-day mortality. Trial registration This is a prospective observational study; therefore, no health care interventions were applied to participants, and trial registration is not applicable.

Gepubliceerd: Crit Care. 2022;26(1):276.
Impact factor: 19.344; Q1

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11. "It Really Is an Elusive Illness"-Post-COVID-19 Illness Perceptions and Recovery Strategies: A Thematic Analysis
Schaap G, Wensink M, Doggen CJM, van der Palen J, Vonkeman HE, Bode C.

A substantial number of patients report persisting symptoms after a COVID-19 infection: so-called post-COVID-19 syndrome. There is limited research on patients' perspectives on post-COVID-19 symptoms and ways to recover. This qualitative study explored the illness perceptions and recovery strategies of patients who had been hospitalised for COVID-19. Differences between recovered and non-recovered patients were investigated. Semi-structured in-depth interviews were held with 24 participating patients (8 recovered and 16 non-recovered) 7 to 12 months after hospital discharge. Data were interpreted using reflexive thematic analysis. Four overarching themes were identified: (I) symptoms after hospital discharge; (II) impact of COVID-19 on daily life and self-identity; (III) uncertainty about COVID-19; and (IV) dealing with COVID-19. Formerly hospitalised post-COVID-19 patients seem to have difficulties with making sense of their illness and gaining control over their recovery. The majority of non-recovered participants continue to suffer mostly from weakness or fatigue, dyspnoea and cognitive dysfunction. No notable differences in illness beliefs were observed between recovered and non-recovered participants.

Gepubliceerd: Int J Environ Res Public Health. 2022;19(20).
Impact factor: 4.614 ; Q1

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12. Generalized pain hypersensitivity and associated factors in gout
Ten Klooster PM, Kraiss JT, Munters R, Vonkeman HE.

Objectives: Previous studies have indicated that a sizeable proportion of patients with inflammatory arthritis present with features characteristic of central pain sensitization. However, this has not yet been examined in patients with gout. The objective of this study was to explore the presence of generalized pain hypersensitivity and associated factors in patients with diagnosed gout**.**
Methods: A cross-sectional survey was performed in outpatients with crystal proven gout using the generalized pain questionnaire (GPQ) to screen for the presence of generalized pain hypersensitivity. Additional self-reported socio-demographic and medical information was collected and several patient-reported outcome measures were completed. Univariable logistic regressions and multivariable LASSO regression analysis with 10-fold cross-validation was used to explore relationships with patient characteristics, clinical features and PROMs**.**
Results: Of the 97 included patients (84.5% male; mean (s.d.) age: 68.9 ± 11.9 years), 20 patients (20.6%, 95% CI: 13.0, 30.0) reported possible generalized pain hypersensitivity defined as a GPQ score ≥11 (range: 0-28; mean (s.d.) GPQ: 6.3 ± 5.3). Lower age, concomitant fibromyalgia and more experienced difficulties in performing their social role were independently associated with generalized pain hypersensitivity. Notably, use of urate lowering therapy was significantly lower in those with generalized pain hypersensitivity.
Conclusions: Generalized pain hypersensitivity appears to be quite common in gout, despite its more intermittent nature compared with other inflammatory arthritides. As this kind of pain does not respond well to regular treatment, screening for non-inflammatory pain may be important for improving pain management in gout.

Gepubliceerd: Rheumatology (Oxford). 2022;61(9):3640-6.
Impact factor: 7.046 ; Q1

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13. Neuropsychiatric adverse drug reactions associated with low dose methotrexate in rheumatoid arthritis patients
Van Lint JA, Bakker T, Ten Klooster PM, van Puijenbroek EP, Vonkeman HE, Jessurun NT.

Background: Neuropsychiatric adverse drug reactions (NPADRs) are not commonly associated with low dose methotrexate (LDMTX) in patients with rheumatoid arthritis (RA).
Research design and methods: In this case series assessment, we described the nature and frequency of NPADRs with LDMTX in the Dutch DREAM-RA registry, including causality of NPADRs, the impact on further LDMTX treatment and the impact on patient reported Health Related Quality of Life (HRQoL)**.**
Results: A total of 71 NPADRs (frequency 6.8%) associated with LDMTX were captured in the DREAM-RA registry. NPADRs were registered for 62 (5.9%) out of 1048 patients with 10.9 NPADRs per 1000 patient years. Headache, dizziness and depression were most frequently reported. The causality was considered probable for 67 NPADRs (94.4%) and definite for 1 NPADR (1.4%). NPADRs led to LDMTX withdrawal in 34 cases (47.9%) and was not restarted in 16 cases (47.1%). Median mental HRQoL was significantly decreased around the occurrence of the NPADR and remained significantly lower after the event. Median physical HRQoL was not significantly affected.
Conclusions: Knowledge on the nature, frequency and impact of the demonstrated NPADRs during LDMTX therapy will enhance attention toward these potential ADRs allowing better risk assessment and communication to patients.

Gepubliceerd: Expert Opin Drug Saf. 2022;21(3):417-23.
Impact factor: 4.011 ; Q2

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14. Hypoglycaemia following JAK inhibitor treatment in patients with diabetes
van Lint JA, van Hunsel F, Tas SW, Vonkeman HE, Hoentjen F, van Doorn MBA, Hebing RCF, Nurmohamed MT, van den Bemt BJF, van Puijenbroek EP, Jessurun NT.

Gepubliceerd: Ann Rheum Dis. 2022;81(4):597-9.
Impact factor: 28.003 ; Q1

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15. Early radiological progression remains associated with long-term joint damage in real-world rheumatoid arthritis patients treated to the target of remission
Versteeg GA, Steunebrink L, Vonkeman HE, Ten Klooster PM, Van Der Bijl AE, Van De Laar M.

Objective: To evaluate radiological damage and to explore characteristics associated with radiological progression in rheumatoid arthritis (RA) treated to the target of remission in a real-world setting**.**
Methods: Baseline to 6 year follow-up data were used from an observational early RA cohort. Radiographs of hands and feet at baseline, 6 months, and 1, 3, and 6 years were scored using the modified Sharp/van der Heijde score (SHS). The threshold for rapid radiological progression (RRP) after 6 months was based on the calculated smallest detectable change of 3.95. Negative binomial generalized linear mixed model and logistic regression analyses were performed to examine which variables were associated with RRP and 6 year radiological progression**.**
Results: Most radiological damage occurred in the first year of treatment [median 2.0 interquartile range (IQR) 1.0-4.0 SHS points] compared to the subsequent 5 years of follow-up (median 3.0 IQR 1.0-5.0 SHS points). While low disease activity was achieved within 6 months on average, 18.8% of the patients developed RRP. Anti-cyclic citrullinated peptide (anti-CCP) positivity [incidence rate ratio (IRR) 1.42, $p = 0.03$], baseline erosive disease (IRR 1.60, $p = 0.02$), and RRP (IRR 3.28, $p < 0.001$) were

associated with 6 year radiological progression. Erosive disease was the strongest predictor of RRP (odds ratio 8.8, p < 0.001)**.**
Conclusion: Long-term radiological outcome is limited in most real-world RA patients treated to the target of remission, but RRP still occurs. Anti-CCP positivity, baseline erosive disease, and RRP remain associated with long-term radiological outcome.

Gepubliceerd: Scand J Rheumatol. 2022;51(2):87-96.
Impact factor: 3.057 ; Q3

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16. Impact of the COVID-19 pandemic on work productivity in patients with spondyloarthritis: results from the Dutch SpA-Net registry
Webers C, van Tubergen A, Vonkeman HE, Boonen A.

Objective: To investigate whether work productivity in patients with spondyloarthritis (SpA) changed following the onset of the COVID-19 pandemic**.**
Methods: Data from the Dutch SpA-Net registry were used. Work productivity was assessed with the Work Productivity and Activity Impairment General Health questionnaire. Proportions of patients employed and their overall work impairment (0%-100%) were compared during a 1-year period before ('pre-pandemic') and a 1-year period after the onset ('post-onset') of the pandemic (March 2020). Generalised estimating equation analysis of all assessments since 2016 explored whether overall work impairment (absenteeism and presenteeism) in employed patients changed with pandemic onset, adjusting for confounders. Similar analyses with disease activity as outcome were used to facilitate interpretation of work productivity results**.**
Results: Data were available during pre-pandemic and post-onset years for 204 patients. Pre-pandemic, 128 (62%) patients were employed. Post-onset, 7 (3.4%) had lost employment, while another 7 (3.4%) originally unemployed gained employment. Overall work impairment was worse following pandemic onset (37.0%) compared with pre-pandemic (27.0%) (p<0.01). Post-onset increase in overall work impairment was mainly observed in patients with lower education (B=9.57, 95% CI 5.63 to 13.51) and largely attributable to absenteeism (B=11.15, 95% CI 7.44 to 14.86). In patients with high education, no such increase was seen. Disease activity did not change with pandemic onset.
Conclusions: Work productivity worsened in patients with SpA after pandemic onset, especially in patients with lower education, while employment losses were limited and disease activity remained stable. Work support should be considered during the COVID-19 pandemic and thereafter for those vulnerable to adverse work outcome.

Gepubliceerd: RMD Open. 2022;8(2).
Impact factor: 5.806 ; Q1

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17. Physical and mental fatigue in post-COVID syndrome and their associations over time: A small-sample ESM-study to explore fatigue, quality of sleep and behaviours
Wensink M, Schaap G, Ten Klooster PM, Doggen CJM, van der Palen J, Vonkeman HE, Bode C.

Objective: Post-COVID syndrome leaves millions of people with severe fatigue, yet little is known about its nature in daily life. In this exploratory study, momentary associations between physical and mental fatigue, quality of sleep and behaviours over two weeks in patients with post-COVID syndrome were assessed.

Method: Data on fatigue levels, quality of sleep and behaviours was collected for 14 consecutive days using the experience sampling method in ten ex-hospitalised patients with post-COVID syndrome**.**
Results: Multilevel linear regression modelling showed strong associations between physical and mental fatigue (β = 0.61, p ≤0.001), significant both between and within individuals. Sleeping more hours at night was associated with less physical and mental fatigue the following day (β = -0.35, p = .001; β = -0.27, p = .008). Strenuous relaxation (B = 0.45, p ≤0.001; B = 0.28, p = .004) and social contacts (B = -0.33, p = .003; B = -0.22, p = .02) were associated with physical and mental fatigue at the same measurement point. Performing household chores decreased physical and mental fatigue (B = -0.29, p = .02; B = -0.30, p = .006) two hours later on the same day, whereas eating and drinking increased physical fatigue (B = 0.20, p = .05) two hours later on the same day**.**
Conclusion: Physical fatigue and mental fatigue were strongly associated and revealed fluctuations in fatigue levels between individuals, which might suggest potentially different post-COVID subgroups. Indications for potential risk and beneficial behaviours for fatigue were found.

Gepubliceerd: J Psychosom Res. 2022;164:111084.
Impact factor: 4.620 ; Q2

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18. TOFA-PREDICT study protocol: a stratification trial to determine key immunological factors predicting tofacitinib efficacy and drug-free remission in psoriatic arthritis (PsA)
Kleinrensink NJ, Perton FT, Pouw JN, Vincken NLA, Hartgring SAY, Jansen MP, Arbabi S, Foppen W, de Jong PA, Tekstra J, Leijten EFA, Spierings J, Lafeber F, Welsing PMJ, Heijstek MW, Tofa-Predict author group; Vonkeman HE, Hettema M

Introduction: Psoriatic arthritis (PsA) is a chronic, inflammatory, musculoskeletal disease that affects up to 30% of patients with psoriasis. Current challenges in clinical care and research include personalised treatment, understanding the divergence of therapy response and unravelling the multifactorial pathophysiology of this complex disease. Moreover, there is an urgent clinical need to predict, assess and understand the cellular and molecular pathways underlying the response to disease-modifying antirheumatic drugs (DMARDs). The TOFA-PREDICT clinical trial addresses this need. Our primary objective is to determine key immunological factors predicting tofacitinib efficacy and drug-free remission in PsA.
Methods and analysis: In this investigator-initiated, phase III, multicentre, open-label, four-arm randomised controlled trial, we plan to integrate clinical, molecular and imaging parameters of 160 patients with PsA. DMARD-naive patients are randomised to methotrexate or tofacitinib. Additionally, patients who are non-responsive to conventional synthetic (cs)DMARDs continue their current csDMARD and are randomised to etanercept or tofacitinib. This results in four arms each with 40 patients. Patients are followed for 1 year. Treatment response is defined as minimal disease activity at week 16. Clinical data, biosamples and images are collected at baseline, 4 weeks and 16 weeks; at treatment failure (treatment switch) and 52 weeks. For the first 80 patients, we will use a systems medicine approach to assess multiomics biomarkers and develop a prediction model for treatment response. Subsequently, data from the second 80 patients will be used for validation.
Ethics and dissemination: The study was approved by the Medical Research Ethics Committee in Utrecht, Netherlands, is registered in the European Clinical Trials Database and is carried out in accordance with the Declaration of Helsinki. The study's progress is monitored by Julius Clinical, a science-driven contract research organisation.
Trial registration number: EudraCT: 2017-003900-28.

Gepubliceerd: BMJ Open. 2022;12(10):e064338.
Impact factor: 3.007; Q2

19. Paediatric COVID-19 mortality: a database analysis of the impact of health resource disparity
Marwali EM, Kekalih A, Yuliarto S, Wati DK, Rayhan M, Valerie IC, Cho HJ, Jassat W, Blumberg L, Masha M, Semple C, Swann OV, Kohns Vasconcelos M, Popielska J, Murthy S, Fowler RA, Guerguerian AM, Streinu-Cercel A, Pathmanathan MD, Rojek A, Kartsonaki C, Goncalves BP, Citarella BW, Merson L, Olliaro PL, Dalton HJ, International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Clinical Characterization Group Investigators; Beishuizen A, Brusse-Keizer M, Delsing C, Haalboom M, Klont R, van der Palen J, van der Valk P, Van Veen H, Vonkeman H

Background: The impact of the COVID-19 pandemic on paediatric populations varied between high-income countries (HICs) versus low-income to middle-income countries (LMICs). We sought to investigate differences in paediatric clinical outcomes and identify factors contributing to disparity between countries.
Methods: The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) COVID-19 database was queried to include children under 19 years of age admitted to hospital from January 2020 to April 2021 with suspected or confirmed COVID-19 diagnosis. Univariate and multivariable analysis of contributing factors for mortality were assessed by country group (HICs vs LMICs) as defined by the World Bank criteria.
Results: A total of 12 860 children (3819 from 21 HICs and 9041 from 15 LMICs) participated in this study. Of these, 8961 were laboratory-confirmed and 3899 suspected COVID-19 cases. About 52% of LMICs children were black, and more than 40% were infants and adolescent. Overall in-hospital mortality rate (95% CI) was 3.3% [=(3.0% to 3.6%), higher in LMICs than HICs (4.0% (3.6% to 4.4%) and 1.7% (1.3% to 2.1%), respectively). There were significant differences between country income groups in intervention profile, with higher use of antibiotics, antivirals, corticosteroids, prone positioning, high flow nasal cannula, non-invasive and invasive mechanical ventilation in HICs. Out of the 439 mechanically ventilated children, mortality occurred in 106 (24.1%) subjects, which was higher in LMICs than HICs (89 (43.6%) vs 17 (7.2%) respectively). Pre-existing infectious comorbidities (tuberculosis and HIV) and some complications (bacterial pneumonia, acute respiratory distress syndrome and myocarditis) were significantly higher in LMICs compared with HICs. On multivariable analysis, LMIC as country income group was associated with increased risk of mortality (adjusted HR 4.73 (3.16 to 7.10)).
Conclusion: Mortality and morbidities were higher in LMICs than HICs, and it may be attributable to differences in patient demographics, complications and access to supportive and treatment modalities.

Gepubliceerd: BMJ Paediatr Open. 2022;6(1).
Impact factor: 2.922; Q2

Totale impact factor: 170.471
Gemiddelde impact factor: 8.972

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 10.009
Gemiddelde impact factor: 5.005

Thoraxcentrum

1. Early aortic growth in acute descending aortic dissection
Berezowski M, Scheumann J, Beyersdorf F, Jasinski M, Plonek T, Siepe M, Czerny M, Rylski B.

Objectives: Acute aortic dissection leads to the destabilization of the aortic wall, followed by an immediate increase in aortic diameter. It remains unclear how the aortic diameter changes during the dissection's acute and subacute phases. The aim of this study was to evaluate the change in aortic geometry within 30 days after the onset of a descending aortic dissection**.**
Methods: Patients with acute type B and non-A non-B dissection who had at least 2 computed tomography angiography scans obtained within 30 days after the onset of dissection were evaluated. Exclusion criteria were a thrombosed false lumen, connective tissue disorders and endovascular or open aortic repair performed prior to the second computed tomography angiography**.**
Results: Among 190 patients with acute aortic dissection, 42 patients met our inclusion criteria. Their aortic geometry was analysed according to the computed tomography angiography scans obtained between 0-3 (N = 35), 4-7 (N = 9) and 8-30 (N = 12) days after the dissection onset. The highest aortic diameter growth rate was observed in the first quartile of the thoracic aorta and measured 0.66 (0.06; 1.03), 0.29 (-0.01; 0.41) and 0.06 (-0.13; 0.26) mm/day at 0-3, 4-7 and 8-30 days after the dissection, respectively. Proximal entry location (P = 0.037) and entry located at the arch concavity (P = 0.008) were associated with a higher aortic diameter increase.
Conclusions: Early rapid growth occurs during the first week after the descending aortic dissection-most intensely over the first 3 days, and this is associated with the location of the dissection's entry.

Gepubliceerd: Interact Cardiovasc Thorac Surg. 2022;34(5):857-64.
Impact factor: 1.978 ; Q4

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2. Specific recommendations (or lack thereof) for older patients with cardiovascular disease in the current European Society of Cardiology guidelines: From the Dutch Working Group of Geriatric Cardiology of the Netherlands Society of Cardiology (NVVC) and Special Interest Group Geriatric Cardiology of the Netherlands Society for Clinical Geriatrics (NVKG)
Boerlage-van Dijk K, Siegers CEP, Wouters N, Faes MC, Verbunt RAM, Geertman JH, van den Heuvel M, van de Meerendonk CTU, Liem SS, Henriques JP, Ottervanger JP.

Due to population ageing, the number of older and frail patients with cardiovascular disease is increasing. In the current guidelines of the European Society of Cardiology specific recommendations for this older population are missing or scarce, probably due to limited evidence concerning diagnosis and treatment of cardiovascular disease in older patients. Moreover, recommendations on shared decision making, palliative care and advanced care planning are also essential in these guidelines. In this article we evaluate the current European of Society of Cardiology guidelines (2013-2020) to determine whether specific recommendations for older patients have been included.

Gepubliceerd: Neth Heart J. 2022;30(12):541-5.
Impact factor: 2.888 ; Q3

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3. Prediction of All-Cause Mortality Following Percutaneous Coronary Intervention in Bifurcation Lesions Using Machine Learning Algorithms
Burrello J, Gallone G, Burrello A, Jahier Pagliari D, Ploumen EH, Iannaccone M, De Luca L, Zocca P, Patti G, Cerrato E, Wojakowski W, Venuti G, De Filippo O, Mattesini A, Ryan N, Helft G, Muscoli S, Kan J, Sheiban I, Parma R, Trabattoni D, Giammaria M, Truffa A, Piroli F, Imori Y, Cortese B, Omedè P,

Conrotto F, Chen SL, Escaned J, Buiten RA, Von Birgelen C, Mulatero P, De Ferrari GM, Monticone S, D'Ascenzo F.

Stratifying prognosis following coronary bifurcation percutaneous coronary intervention (PCI) is an unmet clinical need that may be fulfilled through the adoption of machine learning (ML) algorithms to refine outcome predictions. We sought to develop an ML-based risk stratification model built on clinical, anatomical, and procedural features to predict all-cause mortality following contemporary bifurcation PCI. Multiple ML models to predict all-cause mortality were tested on a cohort of 2393 patients (training, n = 1795; internal validation, n = 598) undergoing bifurcation PCI with contemporary stents from the real-world RAIN registry. Twenty-five commonly available patient-/lesion-related features were selected to train ML models. The best model was validated in an external cohort of 1701 patients undergoing bifurcation PCI from the DUTCH PEERS and BIO-RESORT trial cohorts. At ROC curves, the AUC for the prediction of 2-year mortality was 0.79 (0.74-0.83) in the overall population, 0.74 (0.62-0.85) at internal validation and 0.71 (0.62-0.79) at external validation. Performance at risk ranking analysis, k-center cross-validation, and continual learning confirmed the generalizability of the models, also available as an online interface. The RAIN-ML prediction model represents the first tool combining clinical, anatomical, and procedural features to predict all-cause mortality among patients undergoing contemporary bifurcation PCI with reliable performance.

Gepubliceerd: J Pers Med. 2022;12(6).
Impact factor: 3.508 ; Q2

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4. Cost Analysis From a Randomized Comparison of Immediate Versus Delayed Angiography After Cardiac Arrest

Camaro C, Bonnes JL, Adang EM, Spoormans EM, Janssens GN, van der Hoeven NW, Jewbali LS, Dubois EA, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak R, Vlachojannis GJ, Eikemans BJ, van der Harst P, van der Horst IC, Voskuil M, van der Heijden JJ, Beishuizen B, Stoel M, van der Hoeven H, Henriques JP, Vlaar AP, Vink MA, van den Bogaard B, Heestermans TA, de Ruijter W, Delnoij TS, Crijns HJ, Jessurun GA, Oemrawsingh PV, Gosselink MT, Plomp K, Magro M, Elbers PW, van de Ven PM, Lemkes JS, van Royen N.

Background: In patients with out-of-hospital cardiac arrest without ST-segment elevation, immediate coronary angiography did not improve clinical outcomes when compared with delayed angiography in the COACT (Coronary Angiography After Cardiac Arrest) trial. Whether 1 of the 2 strategies has benefits in terms of health care resource use and costs is currently unknown. We assess the health care resource use and costs in patients with out-of-hospital cardiac arrest**.**
Methods and Results: A total of 538 patients were randomly assigned to a strategy of either immediate or delayed coronary angiography. Detailed health care resource use and cost-prices were collected from the initial hospital episode. A generalized linear model and a gamma distribution were performed. Generic quality of life was measured with the RAND-36 and collected at 12-month follow-up. Overall total mean costs were similar between both groups (EUR 33 575±19 612 versus EUR 33 880±21 044; P=0.86). Generalized linear model: (β, 0.991; 95% CI, 0.894-1.099; P=0.86). Mean procedural costs (coronary angiography and percutaneous coronary intervention, coronary artery bypass graft) were higher in the immediate angiography group (EUR 4384±3447 versus EUR 3028±4220; P<0.001). Costs concerning intensive care unit and ward stay did not show any significant difference. The RAND-36 questionnaire did not differ between both groups**.**
Conclusions: The mean total costs between patients with out-of-hospital cardiac arrest randomly assigned to an immediate angiography or a delayed invasive strategy were similar during the initial hospital stay. With respect to the higher invasive procedure costs in the immediate group, a strategy

awaiting neurological recovery followed by coronary angiography and planned revascularization may be considered. Registration URL: https://trialregister.nl;
Unique identifier: NL4857.

Gepubliceerd: J Am Heart Assoc. 2022;11(5):e022238.
Impact factor: 6.107 ; Q2

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5. Outcomes and regional differences in practice in a worldwide coronary stent registry
Cimci M, Polad J, Mamas M, Iniguez-Romo A, Chevalier B, Abhaichand R, Aminian A, Roguin A, Maluenda G, Angioi M, Cassel G, Kuramitsu S, Jacobs L, Debrus R, Malik F, Hildick-Smith D, Laanmets P, Roffi M, e-ULTIMASTER investigators; von Birgelen C.

Objective: The primary objective was to assess the performance of a new generation thin-strut sirolimus-eluting coronary stent with abluminal biodegradable polymer in an all comer population. The secondary objective was to detail differences in contemporary percutaneous coronary intervention (PCI) practice worldwide**.**
Methods: e-Ultimaster was an all-comer, prospective, global registry (NCT02188355) with independent event adjudication enrolling patients undergoing PCI with the study stent. The primary outcome measure was target lesion failure (TLF) at 1 year, defined as the composite of cardiac death, target vessel myocardial infarction and clinically driven target lesion revascularisation. Data were stratified according to 4 geographical regions**.**
Results: A total of 37 198 patients were enrolled (Europe 69.2%, Asia 17.8%, Africa/Middle East 6.6% and South America/Mexico 6.5%) and 1-year follow-up was available for 35 389 patients (95.1%). One-year TLF occurred in 3.2% of the patients, ranging from 2% (Africa/Middle East) to 4.1% (South America/Mexico). In patients with acute coronary syndrome, potent P2Y(12) inhibitors were prescribed in 48% of patients at discharge, while at 1 year 72% were on any dual antiplatelet therapy. Lipid-lowering treatment was administered in 80.9% and 75.5% of patients at discharge and 1 year, respectively. Regional differences in the profile of the treated patients as well as in PCI practice were reported.
Conclusions: In this investigation with worldwide representation, contemporary PCI using a new generation thin-strut sirolimus-eluting coronary stent with abluminal biodegradable polymer was associated with low 1-year TLF across clinical presentations and continents. Suboptimal adherence to current recommendations around antiplatelet and lipid lowering treatments was detected.

Gepubliceerd: Heart. 2022;108(16):1310-8.
Impact factor: 7.369 ; Q1

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6. The porcine abattoir blood model-Evaluation of platelet function for in-vitro hemocompatibility investigations
Clauser JC, Maas J, Mager I, Halfwerk FR, Arens J.

Background: The major obstacle of blood-contacting medical devices is insufficient hemocompatibility, particularly thrombogenicity and platelet activation. Pre-clinical in-vitro testing allows for the evaluation of adverse thrombogenicity-related events, but is limited, among others, by the availability and quantity of human blood donations. The use of animal blood is an accepted alternative for several tests; however, animal and particularly abattoir blood might present species-specific differences to human blood as well as elevated blood values, and pre-activated platelets due to stressed animals and non-standardized blood collection.

Material & methods: To this end, we investigated porcine abattoir blood in comparison to human donor blood with the focus on platelet pre-activation and remaining activation potential. By means of light transmission aggregometry, aggregation kinetics of platelet rich plasma after stimulation with three different concentrations of each adenosine diphosphate (ADP) (5 µM, 10 µM, 20 µM) and collagen (2.5 µg/ml, 5 µg/ml, 10 µg/ml) were monitored**.**
Results: The activation with collagen revealed no significant differences in platelet behavior of the two species. In contrast, stimulation with ADP resulted in a lower maximum aggregation and a high disaggregation for porcine abattoir blood. The latter is a species-specific phenomenon of porcine platelets. Variations within each study cohort were comparable for human and abattoir pig**.**
Conclusion: The similarities in platelet activation following collagen stimulation and the preservation of the porcine-specific reaction to ADP prove a general functionality of the abattoir blood. This finding provides a first step towards the complete validation of the porcine abattoir blood model.

Gepubliceerd: Artif Organs. 2022;46(5):922-31.
Impact factor: 2.663 ; Q3

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7. Impact of the coronavirus disease 2019 pandemic on volume of thoracic aortic surgery on a national level
de Beaufort HWL, Roefs MM, Daeter EJ, Heijmen RH, Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration; Speekenbrink RGH.

Objectives: The aim of this study was to evaluate the effects of the coronavirus 2019 pandemic on elective and acute thoracic aortic surgery in the Netherlands**.**
Methods: The Netherlands Heart Registration database was used to compare the volume of elective and acute surgery on the thoracic aorta in 2019 and 2020, starting from week 11 in both years. A sub-analysis was done to assess the impact of the pandemic on high-volume and low-volume aortic centres**.**
Results: During the pandemic, the number of elective thoracic aortic operations declined by 18% [incidence rate ratio (IRR) 0.82 [0.73-0.91]; P < 0.01]. The decline in volume of elective surgery was significant in both high-volume (IRR 0.82 [0.71-0.94]; P < 0.01) and low-volume aortic centres (IRR 0.81 [0.68-0.98]; P = 0.03). The overall number of acute aortic operations during the pandemic remained similar to that in 2019 (505 vs 499; P = 0.85), but an increased share of these operations occurred at high-volume centres. The number of acute operations performed in high-volume centres increased by 20% (IRR 1.20 [1.01-1.42]; P = 0.04), while the number of acute operations performed in low-volume centres decreased by 17% (IRR 0.83 [0.69-1.00]; P = 0.04).
Conclusions: The coronavirus 2019 pandemic led to a significant decrease in elective thoracic aortic surgery but did not cause a change in the volume of acute thoracic aortic surgery in the Netherlands. Moreover, the pandemic led to a centralization of care for acute thoracic aortic surgery.

Gepubliceerd: Eur J Cardiothorac Surg. 2022;61(4):854-9.
Impact factor: 4.534 ; Q2

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8. Critical appraisal of technologies to assess electrical activity during atrial fibrillation: a position paper from the European Heart Rhythm Association and European Society of Cardiology Working Group on eCardiology in collaboration with the Heart Rhythm Society, Asia Pacific Heart Rhythm Society, Latin American Heart Rhythm Society and Computing in Cardiology
de Groot NMS, Shah D, Boyle PM, Anter E, Clifford GD, Deisenhofer I, Deneke T, van Dessel P, Doessel O, Dilaveris P, Heinzel FR, Kapa S, Lambiase PD, Lumens J, Platonov PG, Ngarmukos T, Martinez JP, Sanchez AO, Takahashi Y, Valdigem BP, van der Veen AJ, Vernooy K, Casado-Arroyo R, De Potter T,

Dinov B, Kosiuk J, Linz D, Neubeck L, Svennberg E, Kim YH, Wan E, Lopez-Cabanillas N, Locati ET, Macfarlane P.

We aim to provide a critical appraisal of basic concepts underlying signal recording and processing technologies applied for (i) atrial fibrillation (AF) mapping to unravel AF mechanisms and/or identifying target sites for AF therapy and (ii) AF detection, to optimize usage of technologies, stimulate research aimed at closing knowledge gaps, and developing ideal AF recording and processing technologies. Recording and processing techniques for assessment of electrical activity during AF essential for diagnosis and guiding ablative therapy including body surface electrocardiograms (ECG) and endo- or epicardial electrograms (EGM) are evaluated. Discussion of (i) differences in uni-, bi-, and multi-polar (omnipolar/Laplacian) recording modes, (ii) impact of recording technologies on EGM morphology, (iii) global or local mapping using various types of EGM involving signal processing techniques including isochronal-, voltage- fractionation-, dipole density-, and rotor mapping, enabling derivation of parameters like atrial rate, entropy, conduction velocity/direction, (iv) value of epicardial and optical mapping, (v) AF detection by cardiac implantable electronic devices containing various detection algorithms applicable to stored EGMs, (vi) contribution of machine learning (ML) to further improvement of signals processing technologies. Recording and processing of EGM (or ECG) are the cornerstones of (body surface) mapping of AF. Currently available AF recording and processing technologies are mainly restricted to specific applications or have technological limitations. Improvements in AF mapping by obtaining highest fidelity source signals (e.g. catheter-electrode combinations) for signal processing (e.g. filtering, digitization, and noise elimination) is of utmost importance. Novel acquisition instruments (multi-polar catheters combined with improved physical modelling and ML techniques) will enable enhanced and automated interpretation of EGM recordings in the near future.

Gepubliceerd: Europace. 2022;24(2):313-30.
Impact factor: 5.486 ; Q2

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9. Impact of Smoking Status on Mortality in STEMI Patients Undergoing Mechanical Reperfusion for STEMI: Insights from the ISACS-STEMI COVID-19 Registry
De Luca G, Algowhary M, Uguz B, Oliveira DC, Ganyukov V, Zimbakov Z, Cercek M, Jensen LO, Loh PH, Calmac L, Ferrer GRI, Quadros A, Milewski M, Scotto D'Uccio F, von Birgelen C, Versaci F, Ten Berg J, Casella G, Wong Sung Lung A, Kala P, Díez Gil JL, Carrillo X, Dirksen M, Becerra-Munoz VM, Lee MK, Juzar DA, Joaquim RM, Paladino R, Milicic D, Davlouros P, Bakraceski N, Zilio F, Donazzan L, Kraaijeveld A, Galasso G, Arpad L, Lucia M, Vincenzo G, Menichelli M, Scoccia A, Yamac AH, Ugur Mert K, Flores Rios X, Kovarnik T, Kidawa M, Moreu J, Vincent F, Fabris E, Martínez-Luengas IL, Boccalatte M, Bosa Ojeda F, Arellano-Serrano C, Caiazzo G, Cirrincione G, Kao HL, Sanchis Forés J, Vignali L, Pereira H, Manzo S, Ordoñez S, Özkan AA, Scheller B, Lehtola H, Teles R, Mantis C, Antti Y, Silveira JAB, Zoni R, Bessonov I, Savonitto S, Kochiadakis G, Alexopulos D, Uribe CE, Kanakakis J, Faurie B, Gabrielli G, Barrios AG, Bachini JP, Rocha A, Tam FC, Rodriguez A, Lukito AA, Saint-Joy V, Pessah G, Tuccillo A, Cortese G, Parodi G, Bouraghda MA, Kedhi E, Lamelas P, Suryapranata H, Nardin M, Verdoia M.

The so-called "smoking paradox", conditioning lower mortality in smokers among STEMI patients, has seldom been addressed in the settings of modern primary PCI protocols. The ISACS-STEMI COVID-19 is a large-scale retrospective multicenter registry addressing in-hospital mortality, reperfusion, and 30-day mortality among primary PCI patients in the era of the COVID-19 pandemic. Among the 16,083 STEMI patients, 6819 (42.3%) patients were active smokers, 2099 (13.1%) previous smokers, and 7165 (44.6%) non-smokers. Despite the impaired preprocedural recanalization (p < 0.001), active smokers had a significantly better postprocedural TIMI flow compared with non-smokers (p

< 0.001); this was confirmed after adjustment for all baseline and procedural confounders, and the propensity score. Active smokers had a significantly lower in-hospital (p < 0.001) and 30-day (p < 0.001) mortality compared with non-smokers and previous smokers; this was confirmed after adjustment for all baseline and procedural confounders, and the propensity score. In conclusion, in our population, active smoking was significantly associated with improved epicardial recanalization and lower in-hospital and 30-day mortality compared with previous and non-smoking history.

Gepubliceerd: J Clin Med. 2022;11(22).
Impact factor: 4.964 ; Q2

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10. COVID-19 pandemic, mechanical reperfusion and 30-day mortality in ST elevation myocardial infarction

De Luca G, Algowhary M, Uguz B, Oliveira DC, Ganyukov V, Zimbakov Z, Cercek M, Jensen LO, Loh PH, Calmac L, Roura-Ferrer G, Quadros A, Milewski M, Scotto di Uccio F, von Birgelen C, Versaci F, Ten Berg J, Casella G, Wong ASL, Kala P, Diez Gil JL, Carrillo X, Dirksen MT, Becerra-Muñoz VM, Kang-Yin Lee M, Juzar DA, de Moura Joaquim R, Paladino R, Milicic D, Davlouros P, Bakraceski N, Zilio F, Donazzan L, Kraaijeveld AO, Galasso G, Lux A, Marinucci L, Guiducci V, Menichelli M, Scoccia A, Yamac A, Ugur Mert K, Flores Rios X, Kovarnik T, Kidawa M, Moreu J, Flavien V, Fabris E, Lozano Martìnez-Luengas I, Boccalatte M, Bosa Ojeda F, Arellano-Serrano C, Caiazzo G, Cirrincione G, Kao HL, Sanchis Fores J, Vignali L, Pereira H, Manzo-Silberman S, Ordonez S, Özkan AA, Scheller B, Lehtola H, Teles R, Mantis C, Ylitalo A, Brum Silveira JA, Zoni R, Bessonov I, Savonitto S, Kochiadakis G, Alexopoulos D, Uribe C, Kanakakis J, Faurie B, Gabrielli G, Gutiérrez A, Bachini JP, Rocha A, Tam FC, Rodriguez A, Lukito A, Saint-Joy V, Pessah G, Tuccillo B, Cortese G, Parodi G, Bouraghda MA, Kedhi E, Lamelas P, Suryapranata H, Nardin M, Verdoia M.

Objective: The initial data of the International Study on Acute Coronary Syndromes - ST Elevation Myocardial Infarction COVID-19 showed in Europe a remarkable reduction in primary percutaneous coronary intervention procedures and higher in-hospital mortality during the initial phase of the pandemic as compared with the prepandemic period. The aim of the current study was to provide the final results of the registry, subsequently extended outside Europe with a larger inclusion period (up to June 2020) and longer follow-up (up to 30 days)**.**
Methods: This is a retrospective multicentre registry in 109 high-volume primary percutaneous coronary intervention (PPCI) centres from Europe, Latin America, South-East Asia and North Africa, enrolling 16 674 patients with ST segment elevation myocardial infarction (STEMI) undergoing PPPCI in March/June 2019 and 2020. The main study outcomes were the incidence of PPCI, delayed treatment (ischaemia time >12 hours and door-to-balloon >30 min), in-hospital and 30-day mortality**.**
Results: In 2020, during the pandemic, there was a significant reduction in PPCI as compared with 2019 (incidence rate ratio 0.843, 95% CI 0.825 to 0.861, p<0.0001). This reduction was significantly associated with age, being higher in older adults (>75 years) (p=0.015), and was not related to the peak of cases or deaths due to COVID-19. The heterogeneity among centres was high (p<0.001). Furthermore, the pandemic was associated with a significant increase in door-to-balloon time (40 (25-70) min vs 40 (25-64) min, p=0.01) and total ischaemia time (225 (135-410) min vs 196 (120-355) min, p<0.001), which may have contributed to the higher in-hospital (6.5% vs 5.3%, p<0.001) and 30-day (8% vs 6.5%, p=0.001) mortality observed during the pandemic**.**
Conclusion: Percutaneous revascularisation for STEMI was significantly affected by the COVID-19 pandemic, with a 16% reduction in PPCI procedures, especially among older patients (about 20%), and longer delays to treatment, which may have contributed to the increased in-hospital and 30-day mortality during the pandemic.
Trial registration number: NCT04412655.

Gepubliceerd: Heart. 2022;108(6):458-66.
Impact factor: 7.369 ; Q1

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11. Impact of chronic obstructive pulmonary disease on short-term outcome in patients with ST-elevation myocardial infarction during COVID-19 pandemic: insights from the international multicenter ISACS-STEMI registry

De Luca G, Nardin M, Algowhary M, Uguz B, Oliveira DC, Ganyukov V, Zimbakov Z, Cercek M, Okkels Jensen L, Loh PH, Calmac L, Roura Ferrer G, Quadros A, Milewski M, Scotto di Uccio F, von Birgelen C, Versaci F, Ten Berg J, Casella G, Wong Sung Lung A, Kala P, Díez Gil JL, Carrillo X, Dirksen M, Becerra-Munoz VM, Lee MK, Arifa Juzar D, de Moura Joaquim R, Paladino R, Milicic D, Davlouros P, Bakraceski N, Zilio F, Donazzan L, Kraaijeveld A, Galasso G, Lux A, Marinucci L, Guiducci V, Menichelli M, Scoccia A, Yamac AH, Ugur Mert K, Flores Rios X, Kovarnik T, Kidawa M, Moreu J, Flavien V, Fabris E, Martínez-Luengas IL, Boccalatte M, Bosa Ojeda F, Arellano-Serrano C, Caiazzo G, Cirrincione G, Kao HL, Sanchis Forés J, Vignali L, Pereira H, Manzo S, Ordoñez S, Özkan AA, Scheller B, Lehtola H, Teles R, Mantis C, Antti Y, Brum Silveira JA, Zoni R, Bessonov I, Savonitto S, Kochiadakis G, Alexopoulos D, Uribe CE, Kanakakis J, Faurie B, Gabrielli G, Gutierrez Barrios A, Bachini JP, Rocha A, Tam FC, Rodriguez A, Lukito AA, Saint-Joy V, Pessah G, Tuccillo A, Cortese G, Parodi G, Bouraghda MA, Kedhi E, Lamelas P, Suryapranata H, Verdoia M.

Background: Chronic obstructive pulmonary disease (COPD) is projected to become the third cause of mortality worldwide. COPD shares several pathophysiological mechanisms with cardiovascular disease, especially atherosclerosis. However, no definite answers are available on the prognostic role of COPD in the setting of ST elevation myocardial infarction (STEMI), especially during COVID-19 pandemic, among patients undergoing primary angioplasty, that is therefore the aim of the current study**.**
Methods: In the ISACS-STEMI COVID-19 registry we included retrospectively patients with STEMI treated with primary percutaneous coronary intervention (PCI) between March and June of 2019 and 2020 from 109 high-volume primary PCI centers in 4 continents**.**
Results: A total of 15,686 patients were included in this analysis. Of them, 810 (5.2%) subjects had a COPD diagnosis. They were more often elderly and with a more pronounced cardiovascular risk profile. No preminent procedural dissimilarities were noticed except for a lower proportion of dual antiplatelet therapy at discharge among COPD patients (98.9% vs. 98.1%, P = 0.038). With regards to short-term fatal outcomes, both in-hospital and 30-days mortality occurred more frequently among COPD patients, similarly in pre-COVID-19 and COVID-19 era. However, after adjustment for main baseline differences, COPD did not result as independent predictor for in-hospital death (adjusted OR [95% CI] = 0.913[0.658-1.266], P = 0.585) nor for 30-days mortality (adjusted OR [95% CI] = 0.850 [0.620-1.164], P = 0.310). No significant differences were detected in terms of SARS-CoV-2 positivity between the two groups**.**
Conclusion: This is one of the largest studies investigating characteristics and outcome of COPD patients with STEMI undergoing primary angioplasty, especially during COVID pandemic. COPD was associated with significantly higher rates of in-hospital and 30-days mortality. However, this association disappeared after adjustment for baseline characteristics. Furthermore, COPD did not significantly affect SARS-CoV-2 positivity.
Trial registration number: NCT04412655 (2nd June 2020).

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Impact factor: 4.582 ; Q2

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12. Thin-Cap Fibroatheroma Rather Than Any Lipid Plaques Increases the Risk of Cardiovascular Events in Diabetic Patients: Insights From the COMBINE OCT-FFR Trial
Fabris E, Berta B, Roleder T, Hermanides RS, I.Jsselmuiden AJJ, Kauer F, Alfonso F, von Birgelen C, Escaned J, Camaro C, Kennedy MW, Pereira B, Magro M, Nef H, Reith S, Roleder-Dylewska M, Gasior P, Malinowski K, De Luca G, Garcia-Garcia HM, Granada JF, Wojakowski W, Kedhi E.

Background: Autopsy studies have established that thin-cap fibroatheromas (TCFAs) are the most frequent cause of fatal coronary events. In living patients, optical coherence tomography (OCT) has sufficient resolution to accurately differentiate TCFA from thick-cap fibroatheroma (ThCFA) and not lipid rich plaque (non-LRP). However, the impact of OCT-detected plaque phenotype of nonischemic lesions on future adverse events remains unknown. Therefore, we studied the natural history of OCT-detected TCFA, ThCFA, and non-LRP in patients enrolled in the prospective multicenter COMBINE FFR-OCT trial (Combined Optical Coherence Tomography Morphologic and Fractional Flow Reserve Hemodynamic Assessment of Non-Culprit Lesions to Better Predict Adverse Event Outcomes in Diabetes Mellitus Patients)**.**
Methods: In the COMBINE FFR-OCT trial, patients with diabetes and ≥1 lesion with a fractional flow reserve >0.80 underwent OCT evaluation and were clinically followed for 18 months. A composite primary end point of cardiac death, target vessel-related myocardial infarction, target-lesion revascularization, and hospitalization for unstable angina was evaluated in relation to OCT-based plaque morphology**.**
Results: A total of 390 patients (age 67.5±9 years; 63% male) with ≥1 nonischemic lesions underwent OCT evaluation: 284 (73%) had ≥1 LRP and 106 (27%) non-LRP lesions. Among LRP patients, 98 (34.5%) had ≥1 TCFA. The primary end point occurred in 7% of LRP patients compared with 1.9% of non-LRP patients (7.0% versus 1.9%; hazard ratio [HR], 3.9 [95% CI, 0.9-16.5]; P=0.068; log rank-P=0.049). However, within LRP patients, TCFA patients had a much higher risk for primary end point compared with ThCFA (13.3% versus 3.8%; HR, 3.8 [95% CI, 1.5-9.5]; P<0.01), and to non-LRP patients (13.3% versus 1.9%; HR, 7.7 [95% CI, 1.7-33.9]; P<0.01), whereas ThCFA patients had risk similar to non-LRP patients (3.8% versus 1.9%; HR, 2.0 [95% CI, 0.42-9.7]; P=0.38). Multivariable analyses identified TCFA as the strongest independent predictor of primary end point (HR, 6.79 [95% CI, 1.50-30.72]; P=0.013).
Conclusions: Among diabetes patients with fractional flow reserve-negative lesions, patients carrying TCFA lesions represent only one-third of LRP patients and are associated with a high risk of future events while patients carrying LRP-ThCFA and non-LRP lesions portend benign outcomes.
REGISTRATION: URL: https://www. CLINICALTRIALS: gov;
Unique identifier: NCT02989740.

Gepubliceerd: Circ Cardiovasc Interv. 2022;15(5):e011728.
Impact factor: 7.514; Q1

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13. Intraoperative transit time flow measurements during off-pump coronary artery bypass surgery: The impact of coronary stenosis on competitive flow
Halfwerk FR, Spoor P, Mariani S, Hagmeijer R, Grandjean JG.

Background: Combining preoperative angiography findings with intraoperative transit time flow measurements (TTFM) may improve patency of coronary artery bypass grafts. Nevertheless, graft flow might be impaired by native coronary flow based on the severity of stenoses, with inferior long-term outcomes. This study investigates the impact of left anterior descending artery (LAD) stenosis on competitive flow measured in left internal mammary artery (LIMA) grafts during off-pump coronary artery bypass grafting**.**

Methods: Fifty patients were included in this prospective single-center cohort study. LAD stenosis was assessed with quantitative coronary analysis (QCA) and stratified into three groups based on its severity. TTFM of LIMA grafts were performed with LAD open and temporarily occluded. Change in mean graft flow after LAD snaring was the primary endpoint. Secondary endpoints included further TTFM parameters, clinical outcomes, and competitive flow index (CFI), defined as the ratio of mean graft flow with open or closed LAD**.**
Results: Mean LAD stenosis as objectified with QCA was 58 ± 15%. Mean LIMA graft flow increased from 20 ml/min with open LAD to 30 ml/min with snared LAD ($p < .001$). TTFM cut-off values for graft patency improved in 26%-42% of patients after LAD occlusion. Median CFI was 0.66 (IQR: 0.56-0.82). Postoperative myocardial infarction occurred in 2.0% of patients, 120-day mortality was 0%, and 2-year mortality was 6.0%.
Conclusions: Routine snaring of the LAD with CFI calculation during coronary artery bypass grafting is useful to detect significant competitive flow in LIMA grafts, potentially preventing unnecessary intraoperative graft revisions.

Gepubliceerd: J Card Surg. 2022;37(2):305-13.
Impact factor: 1.778 ; Q3

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14. Angiography-derived physiology guidance vs usual care in an All-comers PCI population treated with the healing-targeted supreme stent and Ticagrelor monotherapy: PIONEER IV trial design
Hara H, Serruys PW, O'Leary N, Gao C, Murray A, Breslin E, Garg S, Bureau C, Reiber JH, Barbato E, Aminian A, Janssens L, Rosseel L, Benit E, Campo G, Guiducci V, Casella G, Santarelli A, Franzè A, Diaz VAJ, Iñiguez A, Brugaletta S, Sabate M, Amat-Santos IJ, Amoroso G, Wykrzykowska J, von Birgelen C, Somi S, Liu T, Hofma SH, Curzen N, Trillo R, Ocaranza R, Mathur A, Smits PC, Escaned J, Baumbach A, Wijns W, Sharif F, Onuma Y.

Background: Current ESC guidelines recommend the use of intra-coronary pressure guidewires for functional assessment of intermediate-grade coronary stenoses. Angiography-derived quantitative flow ratio (QFR) is a novel method of assessing these stenoses, and guiding percutaneous coronary intervention (PCI).
Methods/Design: The PIONEER IV trial is a prospective, all-comers, multi-center trial, which will randomize 2,540 patients in a 1:1 ratio to PCI guided by angiography-derived physiology or usual care, with unrestricted use in both arms of the Healing-Targeted Supreme sirolimus-eluting stent (HT Supreme). The stent's fast, biologically healthy, and robust endothelial coverage allows for short dual-antiplatelet therapy (DAPT); hence the antiplatelet regimen of choice is 1-month DAPT, followed by ticagrelor monotherapy. In the angiography-derived physiology guided arm, lesions will be functionally assessed using on-line QFR, with stenting indicated in lesions with a QFR ≤0.80. Post-stenting, QFR will be repeated in the stented vessel(s), with post-dilatation or additional stenting recommended if the QFR<0.91 distal to the stent, or if the delta QFR (across the stent) is >0.05. Usual care PCI is performed according to standard clinical practice. The primary endpoint is a non-inferiority comparison of the patient-oriented composite endpoint (POCE) of all-cause death, any stroke, any myocardial infarction, or any clinically, and physiologically driven revascularization with a non-inferiority risk-difference margin of 3.2%, at 1-year post-procedure. Clinical follow-up will be up to 3 years.
Summary: The PIONEER IV trial aims to demonstrate non-inferiority of QFR-guided PCI to usual care PCI with respect to POCE at 1-year in patients treated with HT Supreme stents and ticagrelor monotherapy. CLINICAL
Trial registration: ClinicalTrials.gov UNIQUE IDENTIFIER: NCT04923191 CLASSIFICATIONS: Interventional Cardiology.

Gepubliceerd: Am Heart J. 2022;246:32-43.
Impact factor: 5.099 ; Q2

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15. Sustained Safety and Performance of a Second-Generation Sirolimus-Eluting Absorbable Metal Scaffold: Long-Term Data of the BIOSOLVE-II First-in-Man Trial at 5 Years
Haude M, Toelg R, Lemos PA, Christiansen EH, Abizaid A, von Birgelen C, Neumann FJ, Wijns W, Ince H, Kaiser C, Lim ST, Escaned J, Eeckhout E, Garcia-Garcia HM, Waksman R.

Background: Permanent drug-eluting stents are associated with a steady increase in late complications attributed to persistent inflammation and poor vessel remodelling. Bioresorbable scaffolds have been developed to overcome such long-term limitations by providing temporary vessel support and disappearing thereafter. We aimed to assess the long-term outcomes of an absorbable metallic scaffold at 5 years**.**
Methods: BIOSOLVE-II is an international, multi-centre, first-in-human study assessing the safety and performance of the sirolimus-eluting absorbable metal scaffold DREAMS 2G (commercial name Magmaris) in patients with a maximum of two de novo lesions. After 3 years, follow-up was extended to 5 years with the endpoints of target lesion failure and rate of definite or probable stent thrombosis**.**
Results: A total of 123 patients with 123 lesions were enrolled. Lesions were 12.6 ± 4.5 mm long and 2.7 ± 0.4 mm in diameter, 43.4% were class B2/C lesions, and calcification was moderate to severe in 10.6%. At 5 years, 5.4% of patients had stable angina and 94.6% had no symptoms or ischaemia. Target lesion failure rate was 8.0% [95% confidence interval:4.2;14.9], reflecting 2 cardiac deaths, 2 target-vessel myocardial infarctions, and 6 clinically driven target lesion revascularizations (TLRs). Only one target lesion failure occurred beyond 3 years: a target-vessel myocardial infarction with clinically driven TLR on post-procedure day 1157. One additional non-cardiac death beyond 3 years due to renal failure was reported on day 1777. No definite or probable scaffold thrombosis was observed**.**
Conclusion: The Magmaris scaffold showed favourable long-term safety and clinical performance with low target lesion failure rates and absence of definite or probable scaffold thrombosis throughout 5 years.

Gepubliceerd: Cardiovasc Revasc Med. 2022;38:106-10.
Impact factor: 0 ; Q NVT

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16. Clinical presentation, disease course, and outcome of COVID-19 in hospitalized patients with and without pre-existing cardiac disease: a cohort study across 18 countries
CAPACITY-COVID Collaborative Consortium and LEOSS Study Group; Delsing CE, Meijs MFL, van Veen H, Vonkeman HE.

Aims: Patients with cardiac disease are considered high risk for poor outcomes following hospitalization with COVID-19. The primary aim of this study was to evaluate heterogeneity in associations between various heart disease subtypes and in-hospital mortality**.**
Methods and Results: We used data from the CAPACITY-COVID registry and LEOSS study. Multivariable Poisson regression models were fitted to assess the association between different types of pre-existing heart disease and in-hospital mortality. A total of 16 511 patients with COVID-19 were included (21.1% aged 66-75 years; 40.2% female) and 31.5% had a history of heart disease. Patients with heart disease were older, predominantly male, and often had other comorbid conditions when compared with those without. Mortality was higher in patients with cardiac disease (29.7%; n = 1545 vs. 15.9%; n = 1797). However, following multivariable adjustment, this difference

was not significant [adjusted risk ratio (aRR) 1.08, 95% confidence interval (CI) 1.02-1.15; P = 0.12 (corrected for multiple testing)]. Associations with in-hospital mortality by heart disease subtypes differed considerably, with the strongest association for heart failure (aRR 1.19, 95% CI 1.10-1.30; P < 0.018) particularly for severe (New York Heart Association class III/IV) heart failure (aRR 1.41, 95% CI 1.20-1.64; P < 0.018). None of the other heart disease subtypes, including ischaemic heart disease, remained significant after multivariable adjustment. Serious cardiac complications were diagnosed in <1% of patients**.**
Conclusion: Considerable heterogeneity exists in the strength of association between heart disease subtypes and in-hospital mortality. Of all patients with heart disease, those with heart failure are at greatest risk of death when hospitalized with COVID-19. Serious cardiac complications are rare during hospitalization.

Gepubliceerd: Eur Heart J. 2022;43(11):1104-20.
Impact factor: 35.855 ; Q1

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17. Age is the main determinant of COVID-19 related in-hospital mortality with minimal impact of pre-existing comorbidities, a retrospective cohort study
Henkens M, Raafs AG, Verdonschot JAJ, Linschoten M, van Smeden M, Wang P, van der Hooft BHM, Tieleman R, Janssen MLF, Ter Bekke RMA, Hazebroek MR, van der Horst ICC, Asselbergs FW, Magdelijns FJH, Heymans SRB, CAPACITY-COVID Collaborative Consortium and LEOSS Study Group; Delsing CE, Meijs MFL, van Veen H, Vonkeman HE.

Background: Age and comorbidities increase COVID-19 related in-hospital mortality risk, but the extent by which comorbidities mediate the impact of age remains unknown**.**
Methods: In this multicenter retrospective cohort study with data from 45 Dutch hospitals, 4806 proven COVID-19 patients hospitalized in Dutch hospitals (between February and July 2020) from the CAPACITY-COVID registry were included (age 69[58-77]years, 64% men). The primary outcome was defined as a combination of in-hospital mortality or discharge with palliative care. Logistic regression analysis was performed to analyze the associations between sex, age, and comorbidities with the primary outcome. The effect of comorbidities on the relation of age with the primary outcome was evaluated using mediation analysis**.**
Results: In-hospital COVID-19 related mortality occurred in 1108 (23%) patients, 836 (76%) were aged ≥70 years (70+). Both age 70+ and female sex were univariably associated with outcome (odds ratio [OR]4.68, 95%confidence interval [4.02-5.45], OR0.68[0.59-0.79], respectively;both p< 0.001). All comorbidities were univariably associated with outcome (p<0.001), and all but dyslipidemia remained significant after adjustment for age70+ and sex. The impact of comorbidities was attenuated after age-spline adjustment, only leaving female sex, diabetes mellitus (DM), chronic kidney disease (CKD), and chronic pulmonary obstructive disease (COPD) significantly associated (female OR0.65[0.55-0.75], DM OR1.47[1.26-1.72], CKD OR1.61[1.32-1.97], COPD OR1.30[1.07-1.59]). Pre-existing comorbidities in older patients negligibly (<6% in all comorbidities) mediated the association between higher age and outcome.
Conclusions: Age is the main determinant of COVID-19 related in-hospital mortality, with negligible mediation effect of pre-existing comorbidities.
Trial registration: CAPACITY-COVID (NCT04325412).

Gepubliceerd: BMC Geriatr. 2022;22(1):184.
Impact factor: 4.070 ; Q2

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18. COMPARE LAAO: Rationale and design of the randomized controlled trial "COMPARing Effectiveness and safety of Left Atrial Appendage Occlusion to standard of care for atrial fibrillation patients at high stroke risk and ineligible to use oral anticoagulation therapy"
Huijboom M, Maarse M, Aarnink E, van Dijk V, Swaans M, van der Heijden J, I.Jsselmuiden S, Folkeringa R, Blaauw Y, Elvan A, Stevenhagen J, Vlachojannis G, van der Voort P, Westra S, Chaldoupi M, Khan M, de Groot J, van der Kley F, van Mieghem N, van Dijk E, Dijkgraaf M, Tijssen J, Boersma L.

Background: Left atrial appendage occlusion (LAAO) provides an alternative to oral anticoagulation (OAC) for stroke prevention in patients with atrial fibrillation (AF). In patients with a long-term or permanent contraindication for OAC randomized controlled trial (RCT) data is lacking. STUDY
Objectives: To assess the efficacy and safety of LAAO in AF patients who are ineligible to use OAC. The co-primary efficacy endpoint is (1) time to first occurrence of stroke (ischemic, hemorrhagic, or undetermined) and (2) time to first occurrence of the composite of stroke, transient ischemic attack (TIA), and systemic embolism (SE). The primary safety endpoint is the 30-day rate of peri-procedural complications.
Study design: This is a multicenter, investigator-initiated, open-label, blinded endpoint (PROBE), superiority-driven RCT. Patients with AF, a CHA_2DS_2-VASc score ≥2 for men and ≥3 for women and a long-term or permanent contraindication for OAC will be randomized in a 2:1 fashion to the device- or control arm. Patients in the device arm will undergo percutaneous LAAO and will receive post-procedural dual antiplatelet therapy (DAPT) per protocol, while those in the control arm will continue their current treatment consisting of no antithrombotic therapy or (D)APT as deemed appropriate by the primary responsible physician. In this endpoint-driven trial design, assuming a 50% lower stroke risk of LAAO compared to conservative treatment, 609 patients will be followed for a minimum of 1 and a maximum of 5 years. Cost-effectiveness and budget impact analyses will be performed to allow decision-making on reimbursement of LAAO for the target population in the Netherlands.
Summary: The COMPARE LAAO trial will investigate the clinical superiority in preventing thromboembolic events and cost-effectiveness of LAAO in AF patients with a high thromboembolic risk and a contraindication for OAC use.
NCT Trial Number: NCT04676880.

Gepubliceerd: Am Heart J. 2022;250:45-56.
Impact factor: 5.099 ; Q2

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19. The influence of timing of coronary angiography on acute kidney injury in out-of-hospital cardiac arrest patients: a retrospective cohort study
Janssens GN, Daemen J, Lemkes JS, Spoormans EM, Janssen D, den Uil CA, Jewbali LSD, Heestermans T, Umans V, Halfwerk FR, Beishuizen A, Nas J, Bonnes J, van de Ven PM, van Rossum AC, Elbers PWG, van Royen N.

Background: Acute kidney injury (AKI) is a frequent complication in cardiac arrest survivors and associated with adverse outcome. It remains unclear whether the incidence of AKI increases after the post-cardiac arrest contrast administration for coronary angiography and whether this depends on timing of angiography. Aim of this study was to investigate whether early angiography is associated with increased development of AKI compared to deferred angiography in out-of-hospital cardiac arrest (OHCA) survivors**.**
Methods: In this retrospective multicenter cohort study, we investigated whether early angiography (within 2 h) after OHCA was non-inferior to deferred angiography regarding the development of AKI. We used an absolute difference of 5% as the non-inferiority margin. Primary non-inferiority analysis was done by calculating the risk difference with its 90% confidence interval (CI) using a generalized linear model for a binary outcome. As a sensitivity analysis, we repeated the primary analysis using

propensity score matching. A multivariable model was built to identify predictors of acute kidney injury**.**
Results: A total of 2375 patients were included from 2009 until 2018, of which 1148 patients were treated with early coronary angiography and 1227 patients with delayed or no angiography. In the early angiography group 18.5% of patients developed AKI after OHCA and 24.1% in the deferred angiography group. Risk difference was - 3.7% with 90% CI ranging from - 6.7 to - 0.7%, indicating non-inferiority of early angiography. The sensitivity analysis using propensity score matching showed accordant results, but no longer non-inferiority of early angiography. The factors time to return of spontaneous circulation (odds ratio [OR] 1.12, 95% CI 1.06-1.19, p < 0.001), the (not) use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (OR 0.20, 95% CI 0.04-0.91, p = 0.04) and baseline creatinine (OR 1.05, 95% CI 1.03-1.07, p < 0.001) were found to be independently associated with the development of AKI.
Conclusions: Although AKI occurred in approximately 20% of OHCA patients, we found that early angiography was not associated with a higher AKI incidence than a deferred angiography strategy. The present results implicate that it is safe to perform early coronary angiography with respect to the risk of developing AKI after OHCA.

Gepubliceerd: Ann Intensive Care. 2022;12(1):12.
Impact factor: 10.318 ; Q1

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20. Bicuspid aortic valve repair with external or subcommissural annuloplasty-echocardiographic prospective trial
Jasinski M, Plonek T, Gocol R, Pysz P, Hudziak D, Wenzel-Jasinska I, Kansy A, Deja M.

Background: The incompetent bicuspid aortic valve (BAV) can be repaired using various techniques. This study presents a prospective comparison of external and subcommissural aortic annuloplasty**.**
Methods: Fifty consecutive patients (38 males, age: 43.9 ± 15.8 years) with BAV insufficiency with or without aortic dilatation underwent valve repair in a single institution. They were prospectively allocated to one of two groups based on the aortic annulus stabilization technique: 25 patients were operated on using the subcommissural annuloplasty (SCA) and 25 using the external complete annuloplasty (EA). Transthoracic echocardiography was performed in all patients before the operation and 1 and 3 years after the operation. Moreover, mortality and morbidity at 7 years were evaluated**.**
Results: In prospective echocardiographic comparison, EA was associated with smaller diameter of the aortic annulus (24.1 ± 2.6 mm vs. 25.8±2.1 mm, p < .05) and lower mean and peak transvalvular gradients (7 ± 4 mmHg vs. 13 ± 4 mmHg, p = .02 and 15.3 ± 9.7 mmHg vs. 20.7 ± 5.6 mmHg, p = .03, respectively). No patients died or required reoperation due to recurrent insufficiency at 6,81 (interquartile range-0,17) years after the operation. The Kaplan-Meier actuarial freedom from aortic regurgitation (AR) grade =2 or gradient > 20 mmHg at 35.1 ± 3.6 months years was 96% (24 out of 25) for patients who had external annuloplasty and amounted to 76% (19 out of 25) for those who had SCA, p = .05).
Conclusions: External annuloplasty performed during repair of the BAV is associated with better hemodynamics at medium-term follow-up compared to SCA.

Gepubliceerd: J Card Surg. 2022;37(3):526-31.
Impact factor: 1.778 ; Q3

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21. Device-related complications in subcutaneous versus transvenous ICD: a secondary analysis of the PRAETORIAN trial

Knops RE, Pepplinkhuizen S, Delnoy P, Boersma LVA, Kuschyk J, El-Chami MF, Bonnemeier H, Behr ER, Brouwer TF, Kaab S, Mittal S, Quast ABE, van der Stuijt W, Smeding L, de Veld JA, Tijssen JGP, Bijsterveld NR, Richter S, Brouwer MA, de Groot JR, Kooiman KM, Lambiase PD, Neuzil P, Vernooy K, Alings M, Betts TR, Bracke F, Burke MC, de Jong J, Wright DJ, Jansen WPJ, Whinnett ZI, Nordbeck P, Knaut M, Philbert BT, van Opstal JM, Chicos AB, Allaart CP, Borger van der Burg AE, Dizon JM, Miller MA, Nemirovsky D, Surber R, Upadhyay GA, Weiss R, de Weger A, Wilde AAM, Olde Nordkamp LRA.

Background: The subcutaneous implantable cardioverter-defibrillator (S-ICD) is developed to overcome lead-related complications and systemic infections, inherent to transvenous ICD (TV-ICD) therapy. The PRAETORIAN trial demonstrated that the S-ICD is non-inferior to the TV-ICD with regard to the combined primary endpoint of inappropriate shocks and complications. This prespecified secondary analysis evaluates all complications in the PRAETORIAN trial**.**
Methods and Results: The PRAETORIAN trial is an international, multicentre, randomized trial in which 849 patients with an indication for ICD therapy were randomized to receive an S- ICD (N = 426) or TV-ICD (N = 423) and followed for a median of 49 months. Endpoints were device-related complications, lead-related complications, systemic infections, and the need for invasive interventions. Thirty-six device-related complications occurred in 31 patients in the S-ICD group of which bleedings were the most frequent. In the TV-ICD group, 49 complications occurred in 44 patients of which lead dysfunction was most frequent (HR: 0.69; P = 0.11). In both groups, half of all complications were within 30 days after implantation. Lead-related complications and systemic infections occurred significantly less in the S-ICD group compared with the TV-ICD group (P < 0.001, P = 0.03, respectively). Significantly more complications required invasive interventions in the TV-ICD group compared with the S-ICD group (8.3% vs. 4.3%, HR: 0.59; P = 0.047)**.**
Conclusion: This secondary analysis shows that lead-related complications and systemic infections are more prevalent in the TV-ICD group compared with the S-ICD group. In addition, complications in the TV-ICD group were more severe as they required significantly more invasive interventions. This data contributes to shared decision-making in clinical practice.

Gepubliceerd: Eur Heart J. 2022;43(47):4872-83.
Impact factor: 35.855 ; Q1

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22. Efficacy and Safety of Appropriate Shocks and Antitachycardia Pacing in Transvenous and Subcutaneous Implantable Defibrillators: Analysis of All Appropriate Therapy in the PRAETORIAN Trial

Knops RE, van der Stuijt W, Delnoy P, Boersma LVA, Kuschyk J, El-Chami MF, Bonnemeier H, Behr ER, Brouwer TF, Kääb S, Mittal S, Quast ABE, Smeding L, Tijssen JGP, Bijsterveld NR, Richter S, Brouwer MA, de Groot JR, Kooiman KM, Lambiase PD, Neuzil P, Vernooy K, Alings M, Betts TR, Bracke F, Burke MC, de Jong J, Wright DJ, Jansen WPJ, Whinnet ZI, Nordbeck P, Knaut M, Philbert BT, van Opstal JM, Chicos AB, Allaart CP, Borger van der Burg AE, Clancy JF, Dizon JM, Miller MA, Nemirovsky D, Surber R, Upadhyay GA, Weiss R, de Weger A, Wilde AAM, Olde Nordkamp LRA.

Background: The PRAETORIAN trial (A Prospective, Randomized Comparison of Subcutaneous and Transvenous Implantable Cardioverter Defibrillator Therapy) showed noninferiority of subcutaneous implantable cardioverter defibrillator (S-ICD) compared with transvenous implantable cardioverter defibrillator (TV-ICD) with regard to inappropriate shocks and complications. In contrast to TV-ICD, S-ICD cannot provide antitachycardia pacing for monomorphic ventricular tachycardia. This prespecified secondary analysis evaluates appropriate therapy and whether antitachycardia pacing reduces the number of appropriate shocks**.**
Methods: The PRAETORIAN trial was an international, investigator-initiated randomized trial that included patients with an indication for implantable cardioverter defibrillator (ICD) therapy. Patients

with previous ventricular tachycardia <170 bpm or refractory recurrent monomorphic ventricular tachycardia were excluded. In 39 centers, 849 patients were randomized to receive an S-ICD (n=426) or TV-ICD (n=423) and were followed for a median of 49.1 months. ICD programming was mandated by protocol. Appropriate ICD therapy was defined as therapy for ventricular arrhythmias. Arrhythmias were classified as discrete episodes and storm episodes (≥3 episodes within 24 hours). Analyses were performed in the modified intention-to-treat population.
Results: In the S-ICD group, 86 of 426 patients received appropriate therapy, versus 78 of 423 patients in the TV-ICD group, during a median follow-up of 52 months (48-month Kaplan-Meier estimates 19.4% and 17.5%; P=0.45). In the S-ICD group, 83 patients received at least 1 shock, versus 57 patients in the TV-ICD group (48-month Kaplan-Meier estimates 19.2% and 11.5%; P=0.02). Patients in the S-ICD group had a total of 254 shocks, compared with 228 shocks in the TV-ICD group (P=0.68). First shock efficacy was 93.8% in the S-ICD group and 91.6% in the TV-ICD group (P=0.40). The first antitachycardia pacing attempt successfully terminated 46% of all monomorphic ventricular tachycardias, but accelerated the arrhythmia in 9.4%. Ten patients with S-ICD experienced 13 electrical storms, versus 18 patients with TV-ICD with 19 electrical storms. Patients with appropriate therapy had an almost 2-fold increased relative risk of electrical storms in the TV-ICD group compared with the S-ICD group (P=0.05).
Conclusions: In this trial, no difference was observed in shock efficacy of S-ICD compared with TV-ICD. Although patients in the S-ICD group were more likely to receive an ICD shock, the total number of appropriate shocks was not different between the 2 groups. Registration: URL: https://www.clinicaltrials.gov;
Unique identifier: NCT01296022.

Gepubliceerd: Circulation. 2022;145(5):321-9.
Impact factor: 39.922; Q1

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23. Utility of the ACC/AHA Lesion Classification to Predict Outcomes After Contemporary DES Treatment: Individual Patient Data Pooled Analysis From 7 Randomized Trials
Konigstein M, Redfors B, Zhang Z, Kotinkaduwa LN, Mintz GS, Smits PC, Serruys PW, von Birgelen C, Madhavan MV, Golomb M, Ben-Yehuda O, Mehran R, Leon MB, Stone GW.

Background: Use of the modified American College of Cardiology (ACC)/American Heart Association (AHA) lesion classification as a prognostic tool to predict short- and long-term clinical outcomes after percutaneous coronary intervention in the modern drug-eluting stent era is uncertain.
Methods and Results: Patient-level data from 7 prospective, randomized trials were pooled. Clinical outcomes of patients undergoing single lesion percutaneous coronary intervention with second-generation drug-eluting stent were analyzed according to modified ACC/AHA lesion class. The primary end point was target lesion failure (TLF: composite of cardiac death, target vessel myocardial infarction, or ischemia-driven target lesion revascularization). Clinical outcomes to 5 years were compared between patients treated for noncomplex (class A/B1) versus complex (class B2/C) lesions. Eight thousand five hundred sixteen patients (age 63.1±10.8 years, 70.5% male) were analyzed. Lesions were classified as A, B1, B2, and C in 7.9%, 28.5%, 33.7%, and 30.0% of cases, respectively. Target lesion failure was higher in patients undergoing percutaneous coronary intervention of complex versus noncomplex lesions at 30 days (2.0% versus 1.1%, P=0.004), at 1 year (4.6% versus 3.0%, P=0.0005), and at 5 years (12.4% versus 9.2%, P=0.0001). By multivariable analysis, treatment of ACC/AHA class B2/C lesions was significantly associated with higher rate of 5-year target lesion failure (adjusted hazard ratio, 1.39 [95% CI, 1.17-1.64], P=0.0001) driven by significantly higher rates of target vessel myocardial infarction and ischemia-driven target lesion revascularization.
Conclusions: In this pooled large-scale analysis, treating complex compared with noncomplex lesions according to the modified ACC/AHA classification with second-generation drug-eluting stent was

associated with worse 5-year clinical outcomes. This historical classification system may be useful in the contemporary era for predicting early and late outcomes following percutaneous coronary intervention.

Gepubliceerd: J Am Heart Assoc. 2022;11(24):e025275.
Impact factor: 6.107 ; Q2

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24. Subcutaneous implantable cardioverter-defibrillators: long-term results of the EFFORTLESS study
Lambiase PD, Theuns DA, Murgatroyd F, Barr C, Eckardt L, Neuzil P, Scholten M, Hood M, Kuschyk J, Brisben AJ, Carter N, Stivland TM, Knops R, Boersma LVA.

Aims: To report 5-year outcomes of EFFORTLESS registry patients with early generation subcutaneous implantable cardioverter-defibrillator (S-ICD) devices**.**
Methods and Results: Kaplan-Meier, trend and multivariable analyses were performed for mortality and late (years 2-5) complications, appropriate shock (AS) and inappropriate shock (IAS) rates. Nine hundred and eighty-four of 994 enrolled patients with diverse diagnoses (28% female, 48 ± 17 years, body mass index 27 ± 6 kg/m2, ejection fraction 43 ± 18%) underwent S-ICD implantation. Median follow-up was 5.1 years (interquartile range 4.7-5.5 years). All-cause mortality was 9.3% (95% confidence interval 7.2-11.3%) at 5 years; 703 patients remained in follow-up on study completion, 171 withdrew including 87 (8.8%) with device explanted, and 65 (6.6%) lost to follow-up. Of the explants, only 20 (2.0%) patients needed a transvenous device for pacing indications. First and final shock efficacy for discrete ventricular arrhythmias was consistent at 90% and 98%, respectively, with storm episode final shock efficacy at 95.2%. Time to therapy remained unaltered. Overall 1- and 5-year complication rates were 8.9% and 15.2%, respectively. Early complications did not predict later complications. There were no structural lead failures. Inappropriate shock rates at 1 and 5 years were 8.7% and 16.9%, respectively. Self-terminating inappropriately sensed episodes predicted late IAS. Predictors of late AS included self-terminating appropriately sensed episodes and earlier AS**.**
Conclusion: In this diverse S-ICD registry population, spontaneous shock efficacy was consistently high over 5 years. Very few patients underwent S-ICD replacement with a transvenous device for pacing indications. Treated and self-terminating arrhythmic episodes predict future shock events, which should encourage more personalized device optimization.

Gepubliceerd: Eur Heart J. 2022;43(21):2037-50.
Impact factor: 35.855 ; Q1

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25. Trends, Advantages and Disadvantages in Combined Extracorporeal Lung and Kidney Support From a Technical Point of View
Martins Costa A, Halfwerk F, Wiegmann B, Neidlin M, Arens J.

Extracorporeal membrane oxygenation (ECMO) provides pulmonary and/or cardiac support for critically ill patients. Due to their diseases, they are at high risk of developing acute kidney injury. In that case, continuous renal replacement therapy (CRRT) is applied to provide renal support and fluid management. The ECMO and CRRT circuits can be combined by an integrated or parallel approach. So far, all methods used for combined extracorporeal lung and kidney support present serious drawbacks. This includes not only high risks of circuit related complications such as bleeding, thrombus formation, and hemolysis, but also increase in technical workload and health care costs. In this sense, the development of a novel optimized artificial lung device with integrated renal support could offer important treatment benefits. Therefore, we conducted a review to provide technical

background on existing techniques for extracorporeal lung and kidney support and give insight on important aspects to be addressed in the development of this novel highly integrated artificial lung device.

Gepubliceerd: Front Med Technol. 2022;4:909990.
Impact factor: 0 ; Q NVT

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26. Persistent phrenic nerve palsy after atrial fibrillation ablation: Follow-up data from The Netherlands Heart Registration
Mol D, Renskers L, Balt JC, Bhagwandien RE, Blaauw Y, van Driel V, Driessen AHG, Elvan A, Folkeringa R, Hassink RJ, Hooft van Huysduynen B, Luermans J, Stevenhagen JY, van der Voort PH, Westra SW, de Groot JR, de Jong J.

Background: Persistent phrenic nerve palsy (PNP) is an established complication of atrial fibrillation (AF) ablation, especially during cryoballoon and thoracoscopic ablation. Data on persistent PNP reversibility is limited because most patients recover <24 h. This study aims to investigate persistent PNP recovery, freedom of PNP-related symptoms after AF ablation and identify baseline variables associated with the occurrence and early PNP recovery in a large nationwide registry study**.**
Methods: In this study, we used data from the Netherlands Heart Registration, comprising data from 9549 catheter and thoracoscopic AF ablations performed in 2016 and 2017. PNP data was available of 7433 procedures, and additional follow-up data were collected for patients who developed persistent PNP**.**
Results: Overall, the mean age was 62 ± 10 years, and 67.7% were male. Fifty-four (0.7%) patients developed persistent PNP and follow-up was available in 44 (81.5%) patients. PNP incidence was 0.07%, 0.29%, 1.41%, and 1.25%, respectively for patients treated with conventional-RF, phased-RF, cryoballoon, and thoracoscopic ablation respectively. Seventy-one percent of the patients fully recovered, and 86% were free of PNP-related symptoms after a median follow-up of 203 (113-351) and 184 (82-359) days, respectively. Female sex, cryoballoon, and thoracoscopic ablation were associated with a higher risk to develop PNP. Patients with PNP recovering ≤180 days had a larger left atrium volume index than those with late or no recovery**.**
Conclusion: After AF ablation, persistent PNP recovers in the majority of patients, and most are free of symptoms. Female patients and patients treated with cryoballoon or thoracoscopic ablation are more prone to develop PNP.

Gepubliceerd: J Cardiovasc Electrophysiol. 2022;33(3):559-64.
Impact factor: 2.942 ; Q3

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27. Low 30-Day Mortality After Atrial Fibrillation Ablation: Results From the Netherlands Heart Registration
Mol D, van der Stoel MD, Balt JC, Bhagwandien RE, Blaauw Y, van Dessel P, van Driel V, Driessen AHG, Elvan A, Hassink RJ, Kemme MJB, Kraaier K, Kuijt WJ, Luermans J, van der Voort PH, Westra SW, de Groot JR, de Jong J.

Gepubliceerd: Can J Cardiol. 2022;38(10):1616-8.
Impact factor: 6.617; Q2

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28. Effect of minimally invasive mitral valve surgery compared to sternotomy on short- and long-term outcomes: a retrospective multicentre interventional cohort study based on Netherlands Heart Registration

Olsthoorn JR, Heuts S, Houterman S, Maessen JG, Sardari Nia P, Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration: Speekenbrink RGH.

Objectives: Minimally invasive mitral valve surgery (MIMVS) has been performed increasingly for the past 2 decades; however, large comparative studies on short- and long-term outcomes have been lacking. This study aims to compare short- and long-term outcomes of patients undergoing MIMVS versus median sternotomy (MST) based on real-world data, extracted from the Netherlands Heart Registration**.**
Methods: Patients undergoing mitral valve surgery, with or without tricuspid valve, atrial septal closure and/or rhythm surgery between 2013 and 2018 were included. Primary outcomes were short-term morbidity and mortality and long-term survival. Propensity score matching analyses were performed**.**
Results: In total, 2501 patients were included, 1776 were operated through MST and 725 using an MIMVS approach. After propensity matching, no significant differences in baseline characteristics persisted. There were no between-group differences in 30-day mortality (1.1% vs 0.7%, P = 0.58), 1-year mortality (2.6% vs 2.1%, P = 0.60) or perioperative stroke rate (1.1% vs 0.6%, P = 0.25) between MST and MIMVS, respectively. An increased rate of postoperative arrhythmia was observed in the MST group (31.3% vs 22.4%, P < 0.001). A higher repair rate was found in the MST group (80.9% vs 76.3%, P = 0.04). No difference in 5-year survival was found between the matched groups (95.0% vs 94.3%, P = 0.49). Freedom from mitral reintervention was 97.9% for MST and 96.8% in the MIMVS group (P = 0.01), without a difference in reintervention-free survival (P = 0.30).
Conclusions: The MIMVS approach is as safe as the sternotomy approach for the surgical treatment of mitral valve disease. However, it comes at a cost of a reduced repair rate and more reinterventions in the long term, in the real-world.

Gepubliceerd: Eur J Cardiothorac Surg. 2022;61(5):1099-106.
Impact factor: 4.534 ; Q2

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29. Minimally invasive approach compared to resternotomy for mitral valve surgery in patients with prior cardiac surgery: retrospective multicentre study based on the Netherlands Heart Registration

Olsthoorn JR, Heuts S, Houterman S, Maessen JG, Sardari Nia P, Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration: Speekenbrink RGH.

Objectives: Mitral valve (MV) surgery after prior cardiac surgery is conventionally performed through resternotomy and associated with increased morbidity and mortality. Alternatively, MV can be approached minimally invasively [minimally invasive mitral valve surgery (MIMVS)], but longer-term follow-up of this approach for MV surgery after prior cardiac surgery is lacking. Therefore, the aim of the current study is to evaluate short- and mid-term outcomes of MIMVS versus MV surgery through resternotomy in patients with prior sternotomy, using a nationwide registry**.**
Methods: Patients undergoing isolated MV surgery after prior cardiac surgery between 2013 and 2018 were included. Primary outcomes were short-term morbidity and mortality and mid-term survival. Cox proportional hazard analysis was used to investigate the association between surgical approach and mortality. Propensity score matching was used to correct for potential confounders**.**
Results: In total, 290 patients underwent MV surgery after prior cardiac surgery, of whom 205 patients were operated through resternotomy and 85 patients through MIMVS. No significant differences in 30-day mortality (3.4% vs 2%, P = 0.99) were observed between both groups. Five-year

survival was 86.3% in the resternotomy group, compared to 89.4% in the MIMVS group (log-rank P = 0.45). In the multivariable analysis, surgical approach showed no relation with mid-term mortality [hazard ratio 0.73 (0.34-1.60); P = 0.44]. A lower incidence of prolonged intubation and new-onset arrhythmia was observed in MIMVS.
Conclusions: MV surgery after prior cardiac surgery has excellent short- and mid-term results in the Netherlands, and MIMVS and resternotomy appear to be equally efficacious. MIMVS is associated with a lower incidence of new-onset arrhythmia and prolonged intubation.

Gepubliceerd: Eur J Cardiothorac Surg. 2022;62(5).
Impact factor: 4.534 ; Q2

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30. Pseudoaneurysm of radial artery after heart catheterisation
Pinxterhuis TH, Hofma SH, da Fonseca CA.

Gepubliceerd: Neth Heart J. 2022;30(2):117-8.
Impact factor: 2.888 ; Q3

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31. Outcome after percutaneous coronary intervention with contemporary stents in patients with concomitant peripheral arterial disease: A patient-level pooled analysis of four randomized trials
Pinxterhuis TH, Ploumen EH, Zocca P, Doggen CJM, Schotborgh CE, Anthonio RL, Roguin A, Danse PW, Benit E, Aminian A, Stoel MG, Linssen GCM, Geelkerken RH, von Birgelen C.

Background and Aims: A considerable number of patients who undergo percutaneous coronary intervention (PCI) also have peripheral arterial disease (PAD) - a signal of more advanced atherosclerosis. After bare metal and early-generation drug-eluting coronary stent implantation, PAD patients showed inferior outcome. As stents and medical treatment were further improved, we aimed to assess the impact of PAD on outcome of PCI with contemporary new-generation stents**.**
Methods: We analyzed 3-year pooled patient-level data from 4 large-scale randomized new-generation stent trials to compare all-comer patients with and without (core lab-verified) history of symptomatic PAD, defined as obstructive lesions in peripheral locations including lower and upper extremities, carotid, vertebral, mesenteric and renal arteries. Main endpoint was target vessel failure: cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization**.**
Results: Of all 9204 patients, 695 (7.6%) had a history of symptomatic PAD. They were older and had more often diabetes, renal failure, hypertension, hypercholesterolemia, and prior stroke. PAD was an independent risk factor for target vessel failure (adjusted-HR:1.42, 95%-CI:1.12-1.73, p = 0.001). Target vessel revascularization (adjusted-HR:1.37, 95%-CI:1.04-1.80, p = 0.026), death (adjusted-HR:1.52, 95%-CI:1.17-1.99, p = 0.002), and major adverse cardiovascular event risks (adjusted-HR:1.36, 95%-CI:1.13-1.64, p = 0.001) were also substantially higher.
Conclusions: A history of symptomatic PAD still allows to simply identify patients with increased risk of unfavorable clinical outcome after PCI, including a higher risk of repeated coronary revascularization, despite using contemporary stents. In clinical practice, this knowledge about higher event risks of PAD patients is helpful both during Heart Team discussions and when informing patients about the procedural risk.

Gepubliceerd: Atherosclerosis. 2022;355:52-9.
Impact factor: 6.851 ; Q1

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32. Use of the Left Radial Artery as Vascular Access for Coronary Angiography and as a Bypass Conduit: A Clinical Dilemma?
Ploumen EH, Halfwerk FR, van der Kolk R, Grandjean JG, von Birgelen C, van Til JA.

Purpose: International coronary revascularization guidelines recommend both, transradial vascular access for coronary angiography/intervention and use of the radial artery as a conduit for coronary artery bypass grafting (CABG). These recommendations may pose a clinical dilemma, as transradial access exposes these arteries to vascular trauma which makes them potentially unsuitable as future grafts. In this study, we investigated the awareness and views of cardiologists on these guideline recommendations**.**
Methods: We performed semi-structured interviews with 50 cardiologists from 19 centers, who regularly perform coronary angiographies or interventions, and outlined clinical scenarios to evaluate their preference of vascular access. In addition, we assessed whether preference was related to sub-specialization**.**
Results: The interviewed cardiologists had 16 ± 9.3 years of professional experience. There were 23 (46%) cardiologists from 7 centers without percutaneous coronary intervention facilities, and 27 (56%) cardiologists from 12 interventional centers. All 50 (100%) cardiologists indicated familiarity with the guidelines, yet 28 (56%) said not to be familiar with the aforementioned dilemma, and 9 (18%) stated there was no dilemma at all. Responses did not differ significantly between interventional (n = 28) and non-interventional (n = 22) cardiologists; however, if the right radial artery was unavailable (e.g., occluded), interventional cardiologists more often said to prefer access via the left radial artery (18/28 (64%) vs. 5/22 (23%), p = 0.001)**.**
Conclusion: More than half of the interviewed cardiologists indicated that they had not realized that left transradial access preceding CABG may preclude later use of this artery as a conduit. Notably, in case of unavailability of the right radial artery, interventional cardiologists preferred left transradial access more often than non-interventional cardiologists.

Gepubliceerd: Cardiovasc Revasc Med. 2022;34:134-9.
Impact factor: 0 ; Q NVT

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33. Final 5-Year Report of the Randomized BIO-RESORT Trial Comparing 3 Contemporary Drug-Eluting Stents in All-Comers
Ploumen EH, Pinxterhuis TH, Buiten RA, Zocca P, Danse PW, Schotborgh CE, Scholte M, Gin R, Somi S, van Houwelingen KG, Stoel MG, de Man HAF, Hartmann M, Linssen GCM, van der Heijden LC, Kok MM, Doggen CJM, von Birgelen C.

Background: In a previous trial, higher 5-year mortality was observed following treatment with biodegradable polymer Orsiro sirolimus-eluting stents (SES). We assessed 5-year safety and efficacy of all-comers as well as patients with diabetes treated with SES or Synergy everolimus-eluting stents (EES) versus durable polymer Resolute Integrity zotarolimus-eluting stents (ZES)**.**
Methods and Results: The randomized BIO-RESORT (Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population) trial enrolled 3514 all-comer patients at 4 Dutch cardiac centers. Patients aged ≥18 years who required percutaneous coronary intervention were eligible. Participants were stratified for diabetes and randomized to treatment with SES, EES, or ZES (1:1:1). The main end point was target vessel failure (cardiac mortality, target vessel myocardial infarction, or target vessel revascularization). Five-year follow-up was available in 3183 of 3514 (90.6%) patients. The main end point target vessel failure occurred in 142 of 1169 (12.7%) patients treated with SES, 130 of 1172 (11.6%) treated with EES, versus 157 of 1173 (14.1%) treated with ZES (hazard ratio [HR], 0.89 [95% CI, 0.71-1.12], P(log-rank)=0.31; and HR, 0.82 [95% CI, 0.65-1.04], P(log-rank)=0.10, respectively). Individual components of target vessel failure showed no

significant between-stent difference. Very late definite stent thrombosis rates were low and similar (SES, 1.1%; EES, 0.6%; ZES, 0.9%). In patients with diabetes, target vessel failure did not differ significantly between stent-groups (SES, 19.8%; EES, 19.2%; versus ZES, 21.1% [P(log-rank)=0.69 and P(log-rank)=0.63]).
Conclusions: Orsiro SES, Synergy EES, and Resolute Integrity ZES showed similar 5-year outcomes of safety and efficacy, including mortality. A prespecified stent comparison in patients with diabetes also revealed no significant differences in 5-year clinical outcomes. Registration URL: https://www.clinicaltrials.gov;
Unique identifier: NCT01674803.

Gepubliceerd: J Am Heart Assoc. 2022;11(22):e026041.
Impact factor: 6.107 ; Q2

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34. Search for Holy Grail of Stent Coating Will Go On
Ploumen EH, von Birgelen C.

Gepubliceerd: Cardiovasc Revasc Med. 2022;42:100-1.
Impact factor: 0 ; Q NVT

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35. Transcatheter aortic valve implantation amid the COVID-19 pandemic: a nationwide analysis of the first COVID-19 wave in the Netherlands
Rooijakkers MJP, Li WWL, Stens NA, Vis MM, Tonino PAL, Timmers L, Van Mieghem NM, den Heijer P, Kats S, Stella PR, Roolvink V, van der Werf HW, Stoel MG, Schotborgh CE, Amoroso G, Porta F, van der Kley F, van Wely MH, Gehlmann H, van Garsse L, Geuzebroek GSC, Verkroost MWA, Mourisse JM, Medendorp NM, van Royen N.

Introduction: The coronavirus disease 2019 (COVID-19) pandemic has put tremendous pressure on healthcare systems. Most transcatheter aortic valve implantation (TAVI) centres have adopted different triage systems and procedural strategies to serve highest-risk patients first and to minimise the burden on hospital logistics and personnel. We therefore assessed the impact of the COVID-19 pandemic on patient selection, type of anaesthesia and outcomes after TAVI.
Methods: We used data from the Netherlands Heart Registration to examine all patients who underwent TAVI between March 2020 and July 2020 (COVID cohort), and between March 2019 and July 2019 (pre-COVID cohort). We compared patient characteristics, procedural characteristics and clinical outcomes.
Results: We examined 2131 patients who underwent TAVI (1020 patients in COVID cohort, 1111 patients in pre-COVID cohort). EuroSCORE II was comparable between cohorts (COVID 4.5 ± 4.0 vs pre-COVID 4.6 ± 4.2, p = 0.356). The number of TAVI procedures under general anaesthesia was lower in the COVID cohort (35.2% vs 46.5%, p < 0.001). Incidences of stroke (COVID 2.7% vs pre-COVID 1.7%, p = 0.134), major vascular complications (2.3% vs 3.4%, p = 0.170) and permanent pacemaker implantation (10.0% vs 9.4%, p = 0.634) did not differ between cohorts. Thirty-day and 150-day mortality were comparable (2.8% vs 2.2%, p = 0.359 and 5.2% vs 5.2%, p = 0.993, respectively).
Conclusions: During the COVID-19 pandemic, patient characteristics and outcomes after TAVI were not different than before the pandemic. This highlights the fact that TAVI procedures can be safely performed during the COVID-19 pandemic, without an increased risk of complications or mortality.

Gepubliceerd: Neth Heart J. 2022;30(11):503-9.
Impact factor: 2.888 ; Q3

36. Ischaemic electrocardiogram patterns and its association with survival in out-of-hospital cardiac arrest patients without ST-segment elevation myocardial infarction: a COACT trials' post-hoc subgroup analysis

Spoormans EM, Lemkes JS, Janssens GN, Soultana O, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak R, Vlachojannis GJ, Eikemans BJW, van der Harst P, van der Horst ICC, Voskuil M, van der Heijden JJ, Beishuizen A, Stoel M, Camaro C, van der Hoeven H, Henriques JP, Vlaar APJ, Vink MA, van den Bogaard B, Heestermans T, de Ruijter W, Delnoij TSR, Crijns H, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, van de Ven PM, van Royen N.

Aims: ST-depression and T-wave inversion are frequently present on the post-resuscitation electrocardiogram (ECG). However, the prognostic value of ischaemic ECG patterns is unknown**.** **Methods and Results:** In this post-hoc subgroup analysis of the Coronary Angiography after Cardiac arrest (COACT) trial, the first in-hospital post-resuscitation ECG in out-of-hospital cardiac arrest patients with a shockable rhythm was analysed for ischaemic ECG patterns. Ischaemia was defined as ST-depression of ≥0.1 mV, T-wave inversion in ≥2 contiguous leads, or both. The primary endpoint was 90-day survival. Secondary endpoints were rate of acute unstable lesions, levels of serum troponin-T, and left ventricular function. Of the 510 out-of-hospital cardiac arrest patients, 340 (66.7%) patients had ischaemic ECG patterns. Patients with ischaemic ECG patterns had a worse 90-day survival compared with those without [hazard ratio 1.51; 95% confidence interval (CI) 1.08-2.12; P = 0.02]. A higher sum of ST-depression was associated with lower survival (log-rank = 0.01). The rate of acute unstable lesions (14.5 vs. 15.8%; odds ratio 0.90; 95% CI 0.51-1.59) did not differ between the groups. In patients with ischaemic ECG patterns, maximum levels of serum troponin-T (μg/L) were higher [0.595 (interquartile range 0.243-1.430) vs. 0.359 (0.159-0.845); ratio of geometric means 1.58; 1.13-2.20] and left ventricular function (%) was worse (44.7 ± 12.5 vs. 49.9 ± 13.3; mean difference -5.13; 95% CI -8.84 to -1.42). Adjusted for age and time to return of spontaneous circulation, ischaemic ECG patterns were no longer associated with survival**.** **Conclusion:** Post-arrest ischaemic ECG patterns were associated with worse 90-day survival. A higher sum of ST-depression was associated with lower survival. Adjusted for age and time to return of spontaneous circulation, ischaemic ECG patterns were no longer associated with survival.

Gepubliceerd: Eur Heart J Acute Cardiovasc Care. 2022;11(7):535-43.
Impact factor: 4.766 ; Q2

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37. Noninfectious sternal wound inflammation after coronary artery bypass grafting in a patient with myelodysplastic syndrome: A no-touch approach

Ten Dam L, Ten Broeke M, Poot AM, Gilbers MD, Halfwerk FR.

Pyoderma gangrenosum (PG) is a rare, chronic inflammatory noninfectious dermatosis. It is associated with underlying systemic or hematological diseases such as myelodysplastic syndrome (MDS) and can be triggered after surgery. Recognition and diagnosis of PG can be difficult as it can mimic a wound infection. Misdiagnosis could lead to invasive procedures which worsen the disease and have possible disastrous aftermath. A 74-year-old male with a history of MDS presents with an atypical sternal wound inflammation. Diagnosis confirmed PG after skin biopsy. No surgical or invasive procedures were performed and the patient was treated on an outpatient basis with prednisolone, clobetasol cream, and cyclosporine. This case shows the importance of a rapid diagnosis of the disease. Awareness is required for the diagnosis of PG in a wound with pronounced

livid borders, without improvement after antibiotic treatment or worsening after debridement. Rapid diagnosis and treatment reduce high healthcare costs, morbidity, and mortality.

Gepubliceerd: J Card Surg. 2022;37(8):2419-22.
Impact factor: 1.778 ; Q3

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38. Pregnancy outcomes in women with a systemic right ventricle and transposition of the great arteries results from the ESC-EORP Registry of Pregnancy and Cardiac disease (ROPAC)
Tutarel O, Baris L, Budts W, Gamal Abd-El Aziz M, Liptai C, Majdalany D, Jovanova S, Frogoudaki A, Connolly HM, Johnson MR, Maggioni AP, Hall R, Roos-Hesselink JW, ROPAC Investigators Group; Wagenaar LJ.

Objective: Cardiac disease is a major cause of maternal mortality. Data regarding pregnancy outcomes in women with a systemic right ventricle (sRV) are scarce. We studied pregnancy outcomes in women with an sRV after the atrial switch procedure for transposition of the great arteries (TGA) or congenitally corrected TGA (CCTGA)**.**
Methods: The ESC EORP Registry of Pregnancy and Cardiac Disease is an international prospective registry of pregnant women with cardiac disease. Pregnancy outcomes (maternal/fetal) in all women with an sRV are described. The primary end point was a major adverse cardiac event (MACE) defined as maternal death, supraventricular or ventricular arrhythmias requiring treatment, heart failure, aortic dissection, endocarditis, ischaemic coronary event and other thromboembolic events**.**
Results: Altogether, 162 women with an sRV (TGA n=121, CCTGA n=41, mean age 28.8±4.6 years) were included. No maternal mortality occurred. In 26 women, at least one MACE occurred, heart failure in 16 (9.8%), arrhythmias (atrial 5, ventricular 6) in 11 (6.7%) and others in 4 (2.5%). Prepregnancy signs of heart failure as well as an sRV ejection fraction <40% were predictors of MACE. One woman experienced fetal loss, while no neonatal mortality was observed. No significant differences were found between women with CCTGA and TGA. In the subset of women who had an echocardiogram before and after pregnancy, no clear deterioration in sRV was observed**.**
Conclusion: The majority of women with an sRV tolerated pregnancy well with a favourable maternal and fetal outcome. Heart failure and arrhythmias were the most common MACE.

Gepubliceerd: Heart. 2022;108(2):117-23.
Impact factor: 7.369 ; Q1

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39. Mobile health adherence for the detection of recurrent recent-onset atrial fibrillation
van der Velden RMJ, Pluymaekers N, Dudink E, Luermans J, Meeder JG, Heesen WF, Lenderink T, Widdershoven J, Bucx JJJ, Rienstra M, Kamp O, van Opstal JM, Kirchhof C, van Dijk VF, Swart HP, Alings M, Van Gelder IC, Crijns H, Linz D.

Objective: The Rate Control versus Electrical Cardioversion Trial 7-Acute Cardioversion versus Wait and See trial compared early to delayed cardioversion for patients with recent-onset symptomatic atrial fibrillation (AF). This study aims to evaluate the adherence to a 4-week mobile health (mHealth) prescription to detect AF recurrences after an emergency department visit**.**
Methods: After the emergency department visit, the 437 included patients, irrespective of randomisation arm (early or delayed cardioversion), were asked to record heart rate and rhythm for 1 min three times daily and in case of symptoms by an electrocardiography-based handheld device for 4 weeks (if available). Adherence was appraised as number of performed measurements per number of recordings asked from the patient and was evaluated for longitudinal adherence consistency. All patients who used the handheld device were included in this subanalysis**.**

Results: 335 patients (58% males; median age 67 (IQR 11) years) were included. The median overall adherence of all patients was 83.3% (IQR 29.9%). The median number of monitoring days was 27 out of 27 (IQR 5), whereas the median number of full monitoring days was 16 out of 27 (IQR 14). Higher age and a previous paroxysm of AF were identified as multivariable adjusted factors associated with adherence.
Conclusions: In this randomised trial, a 4-week mHealth prescription to monitor for AF recurrences after an emergency department visit for recent-onset AF was feasible with 85.7% of patients consistently using the device with at least one measurement per day. Older patients were more adherent.
Trial registration number: NCT02248753.

Gepubliceerd: Heart. 2022;109(1):26-33.
Impact factor: 7.369 ; Q1

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40. Preoperative anaemia and outcome after elective cardiac surgery: a Dutch national registry analysis
Hazen Y, Noordzij PG, Gerritse BM, Scohy TV, Houterman S, Bramer S, Berendsen RR, Bouwman RA, Eberl S, Haenen JSE, Hofland J, Ter Horst M, Kingma MF, Van Klarenbosch J, Klok T, De Korte MPJ, Van Der Maaten J, Spanjersberg AJ, Wietsma NE, van der Meer NJM, Rettig TCD, Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration: Speekenbrink RGH.

Background: Previous studies have shown that preoperative anaemia in patients undergoing cardiac surgery is associated with adverse outcomes. However, most of these studies were retrospective, had a relatively small sample size, and were from a single centre. The aim of this study was to analyse the relationship between the severity of preoperative anaemia and short- and long-term mortality and morbidity in a large multicentre national cohort of patients undergoing cardiac surgery**.**
Methods: A nationwide, prospective, multicentre registry (Netherlands Heart Registration) of patients undergoing elective cardiac surgery between January 2013 and January 2019 was used for this observational study. Anaemia was defined according to the WHO criteria, and the main study endpoint was 120-day mortality. The association was investigated using multivariable logistic regression analysis**.**
Results: In total, 35 484 patients were studied, of whom 6802 (19.2%) were anaemic. Preoperative anaemia was associated with an increased risk of 120-day mortality (adjusted odds ratio [aOR] 1.7; 95% confidence interval [CI]: 1.4-1.9; P<0.001). The risk of 120-day mortality increased with anaemia severity (mild anaemia aOR 1.6; 95% CI: 1.3-1.9; P<0.001; and moderate-to-severe anaemia aOR 1.8; 95% CI: 1.4-2.4; P<0.001). Preoperative anaemia was associated with red blood cell transfusion and postoperative morbidity, the causes of which included renal failure, pneumonia, and myocardial infarction.
Conclusions: Preoperative anaemia was associated with mortality and morbidity after cardiac surgery. The risk of adverse outcomes increased with anaemia severity. Preoperative anaemia is a potential target for treatment to improve postoperative outcomes.

Gepubliceerd: Br J Anaesth. 2022;128(4):636-43.
Impact factor: 11.719 ; Q1

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41. Targeted Temperature Management in Out-of-Hospital Cardiac Arrest With Shockable Rhythm: A Post Hoc Analysis of the Coronary Angiography After Cardiac Arrest Trial
Spoormans EM, Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak R, Vlachojannis GJ, Eikemans BJW, Girbes ARJ, van

der Harst P, van der Horst ICC, Voskuil M, van der Heijden JJ, Beishuizen A, Stoel M, Camaro C, van der Hoeven H, Henriques JP, Vlaar APJ, Vink MA, van den Bogaard B, Heestermans T, de Ruijter W, Delnoij TSR, Crijns H, Jessurun GAJ, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, van de Ven PM, van Royen N, Elbers PWG.

Objectives: The optimal targeted temperature in patients with shockable rhythm is unclear, and current guidelines recommend targeted temperature management with a correspondingly wide range between 32°C and 36°C. Our aim was to study survival and neurologic outcome associated with targeted temperature management strategy in postarrest patients with initial shockable rhythm.
Design: Observational substudy of the Coronary Angiography after Cardiac Arrest without ST-segment Elevation trial. SETTING: Nineteen hospitals in The Netherlands**.**
Patients: The Coronary Angiography after Cardiac Arrest trial randomized successfully resuscitated patients with shockable rhythm and absence of ST-segment elevation to a strategy of immediate or delayed coronary angiography. In this substudy, 459 patients treated with mild therapeutic hypothermia (32.0-34.0°C) or targeted normothermia (36.0-37.0°C) were included. Allocation to targeted temperature management strategy was at the discretion of the physician**.**
Interventions: None**.**
measurements and Main Results: After 90 days, 171 patients (63.6%) in the mild therapeutic hypothermia group and 129 (67.9%) in the targeted normothermia group were alive (hazard ratio, 0.86 [95% CI, 0.62-1.18]; log-rank p = 0.35; adjusted odds ratio, 0.89; 95% CI, 0.45-1.72). Patients in the mild therapeutic hypothermia group had longer ICU stay (4 d [3-7 d] vs 3 d [2-5 d]; ratio of geometric means, 1.32; 95% CI, 1.15-1.51), lower blood pressures, higher lactate levels, and increased need for inotropic support. Cerebral Performance Category scores at ICU discharge and 90-day follow-up and patient-reported Mental and Physical Health Scores at 1 year were similar in the two groups.
Conclusions: In the context of out-of-hospital cardiac arrest with shockable rhythm and no ST-elevation, treatment with mild therapeutic hypothermia was not associated with improved 90-day survival compared with targeted normothermia. Neurologic outcomes at 90 days as well as patient-reported Mental and Physical Health Scores at 1 year did not differ between the groups.

Gepubliceerd: Crit Care Med. 2022;50(2):e129-e42.
Impact factor: 9.296; Q1

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42. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study
Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, Gorog DA, Durdil V, Viethen T, Neumann C, Mundl H, Patel MR, Pacific-Af Investigators; Stevenhagen Y

Background: Direct-acting oral anticoagulant use for stroke prevention in atrial fibrillation is limited by bleeding concerns. Asundexian, a novel, oral small molecule activated coagulation factor XIa (FXIa) inhibitor, might reduce thrombosis with minimal effect on haemostasis. We aimed to determine the optimal dose of asundexian and to compare the incidence of bleeding with that of apixaban in patients with atrial fibrillation.
Methods: In this randomised, double-blind, phase 2 dose-finding study, we compared asundexian 20 mg or 50 mg once daily with apixaban 5 mg twice daily in patients aged 45 years or older with atrial fibrillation, a CHA(2)DS(2)-VASc score of at least 2 if male or at least 3 if female, and increased bleeding risk. The study was conducted at 93 sites in 14 countries, including 12 European countries, Canada, and Japan. Participants were randomly assigned (1:1:1) to a treatment group using an interactive web response system, with randomisation stratified by whether patients were receiving a

direct-acting oral anticoagulant before the study start. Masking was achieved using a double-dummy design, with participants receiving both the assigned treatment and a placebo that resembled the non-assigned treatment. The primary endpoint was the composite of major or clinically relevant non-major bleeding according to International Society on Thrombosis and Haemostasis criteria, assessed in all patients who took at least one dose of study medication. This trial is registered with ClinicalTrials.gov, NCT04218266, and EudraCT, 2019-002365-35.
Findings: Between Jan 30, 2020, and June 21, 2021, 862 patients were enrolled. 755 patients were randomly assigned to treatment. Two patients (assigned to asundexian 20 mg) never took any study medication, resulting in 753 patients being included in the analysis (249 received asundexian 20 mg, 254 received asundexian 50 g, and 250 received apixaban). The mean age of participants was 73.7 years (SD 8.3), 309 (41%) were women, 216 (29%) had chronic kidney disease, and mean CHA(2)DS(2)-VASc score was 3.9 (1.3). Asundexian 20 mg resulted in 81% inhibition of FXIa activity at trough concentrations and 90% inhibition at peak concentrations; asundexian 50 mg resulted in 92% inhibition at trough concentrations and 94% inhibition at peak concentrations. Ratios of incidence proportions for the primary endpoint were 0.50 (90% CI 0.14-1.68) for asundexian 20 mg (three events), 0.16 (0.01-0.99) for asundexian 50 mg (one event), and 0.33 (0.09-0.97) for pooled asundexian (four events) versus apixaban (six events). The rate of any adverse event occurring was similar in the three treatment groups: 118 (47%) with asundexian 20 mg, 120 (47%) with asundexian 50 mg, and 122 (49%) with apixaban.
Interpretation: The FXIa inhibitor asundexian at doses of 20 mg and 50 mg once daily resulted in lower rates of bleeding compared with standard dosing of apixaban, with near-complete in-vivo FXIa inhibition, in patients with atrial fibrillation.
Funding: Bayer.

Gepubliceerd: Lancet. 2022;399(10333):1383-90.
Impact factor: 202.731 ; Q1

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43. Impact of the COVID-19 pandemic on surgical care in the Netherlands
de Graaff MR, Hogenbirk RNM, Janssen YF, Elfrink AKE, Liem RSL, Nienhuijs SW, de Vries JPM, Elshof JW, Verdaasdonk E, Melenhorst J, van Westreenen HL, Besselink MGH, Ruurda JP, van Berge Henegouwen MI, Klaase JM, den Dulk M, van Heijl M, Hegeman JH, Braun J, Voeten DM, Wurdemann FS, Warps AK, Alberga AJ, Suurmeijer JA, Akpinar EO, Wolfhagen N, van den Boom AL, Bolster-van Eenennaam MJ, van Duijvendijk P, Heineman DJ, Wouters M, Kruijff S, Dutch CovidSurg Collaborative Study Group: van Duyn EB Geelkerken RH, de Groot R, Moekotte NL, Stam A, Voshaar A, Halfwerk F.

Background: The COVID-19 pandemic caused disruption of regular healthcare leading to reduced hospital attendances, repurposing of surgical facilities, and cancellation of cancer screening programmes. This study aimed to determine the impact of COVID-19 on surgical care in the Netherlands.
Methods: A nationwide study was conducted in collaboration with the Dutch Institute for Clinical Auditing. Eight surgical audits were expanded with items regarding alterations in scheduling and treatment plans. Data on procedures performed in 2020 were compared with those from a historical cohort (2018-2019). Endpoints included total numbers of procedures performed and altered treatment plans. Secondary endpoints included complication, readmission, and mortality rates.
Results: Some 12 154 procedures were performed in participating hospitals in 2020, representing a decrease of 13.6 per cent compared with 2018-2019. The largest reduction (29.2 per cent) was for non-cancer procedures during the first COVID-19 wave. Surgical treatment was postponed for 9.6 per cent of patients. Alterations in surgical treatment plans were observed in 1.7 per cent. Time from diagnosis to surgery decreased (to 28 days in 2020, from 34 days in 2019 and 36 days in 2018; P < 0.001). For cancer-related procedures, duration of hospital stay decreased (5 versus 6 days; P <

0.001). Audit-specific complications, readmission, and mortality rates were unchanged, but ICU admissions decreased (16.5 versus 16.8 per cent; P < 0.001).
Conclusion: The reduction in the number of surgical operations was greatest for those without cancer. Where surgery was undertaken, it appeared to be delivered safely, with similar complication and mortality rates, fewer admissions to ICU, and a shorter hospital stay.
COVID-19 has had a significant impact on healthcare worldwide. Hospital visits were reduced, operating facilities were used for COVID-19 care, and cancer screening programmes were cancelled. This study describes the impact of the COVID-19 pandemic on Dutch surgical healthcare in 2020. Patterns of care in terms of changed or delayed treatment are described for patients who had surgery in 2020, compared with those who had surgery in 2018-2019. The study found that mainly non-cancer surgical treatments were cancelled during months with high COVID-19 rates. Outcomes for patients undergoing surgery were similar but with fewer ICU admissions and shorter hospital stay. These data provide no insight into the burden endured by patients who had postponed or cancelled operations.

Gepubliceerd: Br J Surg. 2022;109(12):1282-92.
Impact factor: 11.782; Q1

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44. Strategies for low-molecular-weight heparin management in pregnant women with mechanical prosthetic heart valves: A nationwide survey of Dutch practice
Voortman M, Roos JW, Slomp J, van Dijk APJ, Bouma BJ, Sieswerda GTJ, Kiès P, Boer A, Waskowski WM, von Birgelen C, Wagenaar LJ.

Background: In this study we investigated current Dutch practice of low molecular weight heparin (LMWH) treatment in pregnant women with mechanical prosthetic heart valves (MPHV) in order to evaluate how management can be optimized.
Methods: Between December 2020 and February 2021, we conducted a survey among Dutch congenital cardiologists of tertiary centers in the Netherlands. We collected and analyzed written, unstructured, open questionnaires that were send to all 8 specialized pregnancy heart teams.
Results: Response was obtained from all centers (response rate 100%). The preferred LMWHs were nadroparin (62.5%), dalteparin (25%), and enoxaparin (12.5%). After replacing vitamin K antagonist (VKA) with LMWH, 7 centers measured the first anti-Xa level within a week, and 1 center measured anti-Xa levels daily until targeted levels were reached. All centers monitored weekly peak anti-Xa levels (4–6 h post-dose) throughout pregnancy. Four out of 8 centers monitored additional trough (i.e. pre-dose) anti-Xa levels, and 3 of these 4 centers switched to LMWH 3 times daily to achieve target levels when necessary.
Conclusions: In Dutch clinical practice, a considerable variation exists in LMWH management for pregnant women with MPHV. In some centers, LMWH was dosed 3 times daily to maintain target anti-Xa levels. Standardizing treatment strategies would allow systematic assessment in prospective studies.

Gepubliceerd: International Journal of Cardiology Congenital Heart Disease. 2022;9:100676.
Impact Factor: 0; NVT

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45. The QUALITY study, effects of eHealth on anxiety and quality of life for postoperative cardiac surgery patients
ten Dam L, Dijkstra K, Halfwerk F.

Angstklachten na een openhartoperatie zijn veelvoorkomend en gaan gepaard met een verminderde kwaliteit van leven (KvL), een verslechterd revalidatietraject en heropnames. Hartrevalidatie is bewezen effectief in het verlagen van angstgevoelens en depressieve klachten, echter start pas 4-5 weken postoperatief. Binnen de huidige tijdsgeest en op wens van de patiënt wordt eHealth steeds meer toegepast. Binnen het Thorax Centrum Twente (TCT) is daarom de CureYou© applicatie ontwikkeld en ingezet ter aanvulling op de hartrevalidatie. Van december 2020 t/m maart 2021 is een longitudinaal onderzoek uitgevoerd naar de effectiviteit van deze applicatie op angstklachten en ervaren KvL. De resultaten laten zien dat postoperatieve angst laag was in zowel de controle en telerevalidatiegroep en deze nam niet extra af in de telerevalidatiegroep. Telerevalidatie met alleen informatievoorziening zonder persuasieve elementen is in de studiepopulatie onvoldoende gebleken om ervaren KvL te verbeteren.

Gepubliceerd: Coridaal. 2022;44(3):82-5.
Impact factor: 0; NVT

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46. A Movement-Artefact-Free Heart-Rate Prediction System
Thoonen M, Veltink P, Halfwerk F, van Delden R, Wang Y.

Continuous automatic heart rate (HR) monitoring plays a crucial role in timely intervention for postoperative patients. However, for effective alarm management, patients' activities of daily living need to be considered as they influence HR. This explorative study aimed to develop a heartrate prediction system while performing six activities. An experiment with fourteen participants was conducted to gather data to build a system. This system consisted of a support-vector machine classifier for activity recognition and a k-Nearest Neighbors regressor for HR prediction. The R-squared (a goodness-of-fit measure) of the HR predictor is 79% on average. Given the heterogeneity of different populations, the system will be further tested and developed using patient datasets in future towards clinical-practice applications.

Gepubliceerd: Computing in Cardiology. 2022;49:1-4.
Impact factor: 0; NVT

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47. Controlled Helical Propulsion Against the Flow of a Physiological Fluid
Li C, Halfwerk F, Arens J, Misra S, Warlé M, Khalil ISM.

Untethered helical magnetic devices (UHMDs) have the potential to navigate bodily fluids using permanent-magnet robotic systems for minimally invasive diagnostic and surgical procedures. These devices can be actuated by robotically moving rotating permanent magnets (RPMs) to achieve controllable steering and propulsion simultaneously in a wireless manner. To date, the vast majority of motion control systems using UHMDs are constrained to operate in the absence of a dynamic flow field and prior work did not rigorously address the fundamental roles of rheological, magnetic, and geometric characteristics of the UHMD and its surroundings on the resulting stability. In this work, we show how to construct the region of attraction of a UHMD driven by two synchronized RPMs inside fluid-filled lumen around an equilibrium point. We first present the governing hydrodynamic model of a magnetically-driven UHMD to describe its behavior against the flow of blood serum. Then we validate the model using 1-D frequency response characterization and show that it captures the measured linear relationship between the actuation frequency and propulsive thrust at various flow fields. We find that a region of asymptotic stability can be achieved around an equilibrium point allowing a 6-mm-long UHMD to overcome maximum volumetric flow field of 1.2 l/hr (i.e., 2.65 cm/s).

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Waardegedreven zorg

1. Self-management interventions for people with chronic obstructive pulmonary disease
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Background: Self-management interventions help people with chronic obstructive pulmonary disease (COPD) to acquire and practise the skills they need to carry out disease-specific medical regimens, guide changes in health behaviour and provide emotional support to enable them to control their disease. Since the 2014 update of this review, several studies have been published.
Objectives: Primary objectives To evaluate the effectiveness of COPD self-management interventions compared to usual care in terms of health-related quality of life (HRQoL) and respiratory-related hospital admissions. To evaluate the safety of COPD self-management interventions compared to usual care in terms of respiratory-related mortality and all-cause mortality. Secondary objectives To evaluate the effectiveness of COPD self-management interventions compared to usual care in terms of other health outcomes and healthcare utilisation. To evaluate effective characteristics of COPD self-management interventions.
Search methods: We searched the Cochrane Airways Trials Register, CENTRAL, MEDLINE, EMBASE, trials registries and the reference lists of included studies up until January 2020.
Selection criteria: Randomised controlled trials (RCTs) and cluster-randomised trials (CRTs) published since 1995. To be eligible for inclusion, self-management interventions had to include at least two intervention components and include an iterative process between participant and healthcare provider(s) in which goals were formulated and feedback was given on self-management actions by the participant.
Data collection and analysis: Two review authors independently selected studies for inclusion, assessed trial quality and extracted data. We resolved disagreements by reaching consensus or by involving a third review author. We contacted study authors to obtain additional information and missing outcome data where possible. Primary outcomes were health-related quality of life (HRQoL), number of respiratory-related hospital admissions, respiratory-related mortality, and all-cause mortality. When appropriate, we pooled study results using random-effects modelling meta-analyses. MAIN RESULTS: We included 27 studies involving 6008 participants with COPD. The follow-up time ranged from two-and-a-half to 24 months and the content of the interventions was diverse. Participants' mean age ranged from 57 to 74 years, and the proportion of male participants ranged from 33% to 98%. The post-bronchodilator forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio of participants ranged from 33.6% to 57.0%. The FEV1/FVC ratio is a measure used to diagnose COPD and to determine the severity of the disease. Studies were conducted on four different continents (Europe (n = 15), North America (n = 8), Asia (n = 1), and Oceania (n = 4); with one study conducted in both Europe and Oceania). Self-management interventions likely improve HRQoL, as measured by the St. George's Respiratory Questionnaire (SGRQ) total score (lower score represents better HRQoL) with a mean difference (MD) from usual care of -2.86 points (95% confidence interval (CI) -4.87 to -0.85; 14 studies, 2778 participants; low-quality evidence). The pooled MD of -2.86 did not reach the SGRQ minimal clinically important difference (MCID) of four points. Self-management intervention participants were also at a slightly lower risk for at least one respiratory-related hospital admission (odds ratio (OR) 0.75, 95% CI 0.57 to 0.98; 15 studies, 3263 participants; very low-quality evidence). The number needed to treat to prevent one respiratory-related hospital admission over a mean of 9.75 months' follow-up was 15 (95% CI 8 to 399) for participants with high baseline risk and 26 (95% CI 15 to 677) for participants with low baseline risk. No differences were observed in respiratory-related mortality (risk difference (RD) 0.01, 95% CI -0.02 to 0.04; 8 studies, 1572 participants ; low-quality evidence) and all-cause mortality (RD -0.01, 95% CI -0.03 to 0.01; 24 studies, 5719 participants; low-quality evidence). We graded the evidence to be of 'moderate' to 'very low' quality according to GRADE. All studies had a substantial risk of bias, because of lack of blinding of participants and personnel to the interventions,

which is inherently impossible in a self-management intervention. In addition, risk of bias was noticeably increased because of insufficient information regarding a) non-protocol interventions, and b) analyses to estimate the effect of adhering to interventions. Consequently, the highest GRADE evidence score that could be obtained by studies was 'moderate'.
Conclusions: Self-management interventions for people with COPD are associated with improvements in HRQoL, as measured with the SGRQ, and a lower probability of respiratory-related hospital admissions. No excess respiratory-related and all-cause mortality risks were observed, which strengthens the view that COPD self-management interventions are unlikely to cause harm. By using stricter inclusion criteria, we decreased heterogeneity in studies, but also reduced the number of included studies and therefore our capacity to conduct subgroup analyses. Data were therefore still insufficient to reach clear conclusions about effective (intervention) characteristics of COPD self-management interventions. As tailoring of COPD self-management interventions to individuals is desirable, heterogeneity is and will likely remain present in self-management interventions. For future studies, we would urge using only COPD self-management interventions that include iterative interactions between participants and healthcare professionals who are competent using behavioural change techniques (BCTs) to elicit participants' motivation, confidence and competence to positively adapt their health behaviour(s) and develop skills to better manage their disease. In addition, to inform further subgroup and meta-regression analyses and to provide stronger conclusions regarding effective COPD self-management interventions, there is a need for more homogeneity in outcome measures. More attention should be paid to behavioural outcome measures and to providing more detailed, uniform and transparently reported data on self-management intervention components and BCTs. Assessment of outcomes over the long term is also recommended to capture changes in people's behaviour. Finally, information regarding non-protocol interventions as well as analyses to estimate the effect of adhering to interventions should be included to increase the quality of evidence.

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