Medisch Spectrum Twente

Medical School Twente

Wetenschappelijk onderzoek MST 2023

MES-7 09 23®

een santeon ziekenhuis

Wetenschappelijk onderzoek in Medisch Spectrum Twente

2023

Inhoudsopgave

Voorwoord

Voor u ligt de 15e editie van het jaarlijks overzicht van de wetenschappelijke publicaties van medewerkers van Medisch Spectrum Twente. Het betreft het jaar 2023. Dit jaaroverzicht wordt ook buiten MST verspreid onder huisartsen, apothekers, fysiotherapeuten, onze collega STZ ziekenhuizen en wetenschappelijke instellingen in de regio.

De publicaties zijn alfabetisch gegroepeerd op vakgroep/maatschap. Hierbij is als criterium genomen dat de publicatie terug te vinden moet zijn op PubMed met publicatiedatum in 2023 ('print date'). De zogenaamde "Epub Ahead of Print" artikelen komen in de volgende uitgave. Daarnaast worden ook peer-reviewed artikelen uit Nederlandstalige tijdschriften opgenomen.

In 2023 zijn 282 unieke publicaties verschenen in peer-reviewed tijdschriften. Ten opzichte van vorig jaar hebben we flink minder gepubliceerd. Een mogelijke verklaring hiervoor zou kunnen zijn dat we door COVID-19 in 2021 en 2022 een flinke piek in publicaties hadden en in 2023 juist te maken hadden met beperkte tijd voor wetenschap door 'in te halen zorg'. We zitten nog wel fors hoger dan pre-COVID.

De gemiddelde impact factor van de artikelen uit 2023 was echter wel zeer hoog met 8.9, wat in de buurt komt van ons absolute record van 9.9 uit 2022. Een knappe prestatie, aangezien de impact factors van journals in 2023 een stuk lager lag, wat ook weer aan COVID te danken lijkt te zijn. Ter vergelijking: the Lancet had in 2022 een impact factor van 202 en in 2023 was dat 98.4. We hebben dit jaar 9 keer in een toptijdschrift gepubliceerd: 4 keer in the Lancet (impact factor 98.4), 3 keer in een subjournal van the Lancet en 2 keer in the New England Journal of Medicine (158.5). De mediane impact factor was dit jaar vergelijkbaar met vorig jaar: 4.1 ten opzichte van 4.6 in 2022.

In het overzicht wordt per publicatie ook weergeven in welk kwartiel het tijdschrift staat in de betreffende categorie. Indien meerdere categorieën van toepassing zijn wordt het hoogste kwartiel genomen. We publiceerden 52% in Q1, 23% in Q2, 11% in Q3 en 3% in Q4. Bij 11% van de artikelen was geen indeling in kwartielen beschikbaar. Qua promoties was 2023 een matig jaar. Binnen MST waren maar 3 promoties. De verwachting is dat veel promovendi hun promotie hebben uitgesteld tot 2024, door vertragingen die zij hebben opgelopen door COVID-19.

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 2023 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 impact factors

Tabel 1. Statistieken unieke publicaties in peer-reviewed tijdschriften met medewerkers van MST als (co-)auteur

	2019	2020	2021	2022	2023
Unieke publicaties	232	239	334	383	282
Gemiddelde impact factor	6.1	5.8	6.5	9.9	8.9
Mediane impact factor	3.2	3.4	3.9	4.6	4.1

Tabel 2. Top 3 afdelingen MST met betrekking tot aantal publicaties, totale impact factor, gemiddelde impact factor van 2020 – 2023

	2020		2021		2022		2023	
Aantal publicaties:								
1	Cardiologie	40	Neurocentrum	52	Heelkunde	67	Neurocentrum	49
2	Med. School	29	Thoraxcentrum	47	Neurocentrum	52	Heelkunde	43
3	Neurocentrum	29	Heelkunde	43	Thoraxcentrum	47	Thoraxcentrum	35
Totale impact factor score:								
1	Cardiologie	433	Neurocentrum	442	Neurocentrum	713	Neurocentrum	622
2	Interne gnkd	169	Thoraxcentrum	346	Intensive care	647	Intensive care	409
3	MDL	145	Intensive care	307	Heelkunde	561	Interne gnkd	371
Gemiddelde impact factor score:								
1	Oogheelknde	17.7	Microbiologie	25.1	Intensive care	17.5	Radiotherapie	17.4
2	Radiotherapie	11.4	Radiologie	17.9	Interne gnkd	17.0	Intensive care	14.6
3	Cardiologie	10.8	MDL	11.2	Radiologie	16.6	Interne & NeuroC	12.8
Aantal publicaties als 1e, 2e of laatste auteur:								
1	Neurocentrum	15	Neurocentrum	23	Heelkunde	18	Neurocentrum	12
2	Cardiologie	14	Thoraxcentrum	14	Neurocentrum	15	Thoraxcentrum	10
3	Med. School	10	Longziekten	10	Thoraxcentrum	12	Heelkunde Plastische chir	8
Totale impact factor score als 1e, 2e of laatste auteur:								
1	Interne gnkd	63	Neurocentrum	85	Heelkunde	85	Thoraxcentrum	120
2	Neurocentrum	61	Thoraxcentrum	44	Klin. farmacie	78	Neurocentrum	49
3	Cardiologie	48	Klin. Chemie	33	Neurocentrum	75	Heelkunde	24
Gemiddelde impact factor score als 1e, 2e of laatste auteur:								
1	Oogheelknde	17.7	MDL	8.0	Klin. farmacie	9.8	Thoraxcentrum	12.0
2	Interne gnkd	11	KNO	5.4	Klin. chemie	9.6	Anesthesie Radiotherapie	8.8
3	Intensive care	9.3	MKA chirurgie	5.4	Anesthesie	7.9	Kindergeneesknd	7.4

Overzicht aantal publicaties per vakgroep

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Anesthesie	0	2	0	1	0	1	4	2	6	1
Cardiologie	25	28	39	31	40	27	40	-	-	-
Dermatologie	0	0	0	0	0	1	0	1	1	0
Gynaecologie	7	6	4	13	7	6	6	5	8	3
Heelkunde	21	31	26	30	20	39	23	43	67	43
Intensive Care	13	14	13	20	15	12	11	33	37	28
Interne Geneeskunde	20	17	8	11	24	14	27	35	39	29
Kindergeneeskunde	3	11	6	6	8	3	11	8	7	6
Klinische Chemie	6	7	5	5	7	4	8	12	12	3
Klinische Farmacie	6	8	10	3	8	13	7	14	12	3
Klinische Fysica	0	2	0	2	1	0	0	2	2	0
Klinische Psychologie	4	1	0	1	2	1	0	0	1	1
KNO	1	1	1	0	0	0	0	1	1	3
Longgeneeskunde	12	16	19	24	28	14	17	22	20	17
MDL	11	5	9	10	5	14	14	16	19	11
Medical School Twente	33	35	33	26	24	24	29	19	35	23
Microbiologie	2	2	4	3	1	2	0	1	12	7
MKA chirurgie	0	0	1	0	1	0	0	1	3	3
Neurochirurgie	5	9	5	5	4	3	-	-	-	-
Neurologie	39	33	41	28	30	33	-	-	-	-
Neurocentrum	-	-	-	-	-	-	29	52	52	49
Nucleaire Geneeskunde	0	2	0	0	0	0	0	0	0	0
Oogheelkunde	0	0	0	0	1	0	1	1	0	0
Orthopedie	4	7	5	4	2	5	3	13	16	8
Pathologie	5	8	4	9	3	4	0	0	1	0
Plastische Chirurgie	0	2	4	4	13	12	11	16	23	16
Psychiatrie	0	1	0	4	0	0	1	0	0	0
Raad van Bestuur	0	0	0	0	0	9	10	7	8	10
Radiologie	11	14	10	4	11	2	4	9	20	21
Radiotherapie	5	12	10	4	5	4	5	6	13	9
Reumatologie	20	23	15	7	15	17	11	10	19	23
Revalidatiegeneeskunde	8	6	0	0	1	0	0	0	0	0
Cardiologie	*25*	*28*	*39*	*31*	*40*	*27*	*40*	-	-	-
Thoraxchirurgie	3	2	4	5	4	3	8	-	-	-
Thoraxcentrum	-	-	-	-	-	-	-	47	47	35
Urologie	0	0	0	0	1	0	0	1	0	0
Waardegedreven zorg	-	-	-	-	-	-	-	4	1	1

Promoties

Heelkunde

ENDOVASCULAR REPAIR OF THE AORTA:
STENTGRAFT DEFORMATION MATTERS

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 14th of April 2023 at 14.45 hours

by

Jaimy Ashley Simmering
Born on the 20th of August, 1994
In Almelo, The Netherlands

Promotors:	Prof. Dr. R.H. Geelkerken
	Prof. Dr. C.H. Slump
Co-promotor:	Dr. E. Groot Jebbink

Samenvatting
Hart- en vaatziekten, waaronder aneurysmatische aandoeningen, blijven doodsoorzaak nummer twee in Nederland. Een aorta aneurysma (AA) is een lokale verwijding van de aorta van minimaal 1,5 keer de oorspronkelijke diameter. AAs ontwikkelen zich meestal onder de nierslagaders (infrarenaal) in de abdominale aorta, oftewel als een abdominaal aorta-aneurysma (AAA). Een ruptuur van een AA veroorzaakt een grote inwendige bloeding en wordt daarom geassocieerd met sterftecijfers tot 80%. Om een ruptuur te voorkomen, worden de AAs behandeld volgens een open chirurgische reparatie (OSR) of een endovasculaire aneurysma reparatie (EVAR). EVAR is volgens de Europese Vereniging voor Vaatchirurgie (ESVS) de gouden standaard geworden voor de behandeling van infrarenale AAA's, terwijl het Britse Nationale Instituut voor Gezondheid en Zorg Excellentie (NICE) adviseert om EVAR alleen in selecte gevallen te overwegen. Deze terughoudendheid van de NICE om EVAR als de eerste keuze in AAA-behandeling te stellen, zoals de ESVS dit wel doet, heeft te maken met het aantal complicaties en reïnterventies tijdens de follow-up die het succes van de behandeling belemmeren. Zo wordt EVAR voor infrarenale AAA geassocieerd met reïnterventiepercentages van 8-20%, die zelfs oplopen tot 12-44% voor gefenestreerde EVAR (FEVAR) voor pararenale AAA. Voor iliac branched devices (IBD) en thoracale EVAR (TEVAR) worden reïnterventiepercentages tussen 10-20% gerapporteerd. De reden voor deze hoge reïnterventiepercentages is het falen van de stentgraft, wat zich kan uiten als endolekkage, stentgraftmigratie, (gedeeltelijke) stentgraftocclusie en uiteindelijk AA ruptuur. Om de resultaten van EVAR in het algemeen te verbeteren, moeten we eerst het gedrag van de verschillende stentgrafts beter begrijpen. Verschillende factoren kunnen de duurzaamheid van deze behandelingen beïnvloeden, waaronder de hartcyclus, de ademhalingscyclus, de lichaamshouding en -positie, de bloedstroming en de samen- stelling van het bloed en de vaatwand. Deze factoren kunnen invloed hebben op, of kunnen worden beïnvloed door, stentgraftdeformatie. **Stentgraftdeformatie** kan worden gedefinieerd als elke verandering in vorm, geometrie en/of dimensie van de stentgraft in de tijd, bijvoorbeeld veranderingen in diameter (expansie) en kromming (curvatuur). Het doel van dit proefschrift was om ons begrip van het in situ gedrag van verschillende stent- graftplatforms voor verschillende soorten AA's te vergroten, in het specifiek de stentgraft-deformatie tijdens de hartcyclus en tijdens de follow-up. Dergelijke deformatie kan worden gekwantificeerd met behulp van elektrocardiogram (ECG)-gated computertomografie (CT) scans.

In **Hoofdstuk 2** werd onderzocht in hoeverre de kwantificatie van hartslag-geïnduceerde stentgraftbeweging vergelijkbaar is wanneer de ECG-gated CT scans gereconstrueerd zijn in 8 of 10 fasen van de hartcyclus. Ook werd de kwantificatie van hartslag-geïnduceerde stentgraftbeweging onderzocht op twee CT-scanners van verschillende fabrikanten. De resultaten toonden aan dat de kwantificering van de stentgraftbeweging bijna identiek is voor de reconstructietypes van ECG-gated CT scans en de verschillende scanners. De verschillen tussen scanreconstructies en scannertypen blijven onder de 0,3 mm, wat aangeeft dat de kwantificatie van de verplaatsing nu wordt belemmerd door de resolutie van de CT-scan.

In **Hoofdstuk 3** hebben we ons verdiept in het gedrag van de pootjes van een specifieke EVAR-stentgraft: het Anaconda-stentgraftsysteem. Het flexibele ontwerp van de Anacondapootjes met afzonderlijke stentringen onderscheidt het van andere veelgebruikte stentgrafts. Het ontwerp bootst in zekere zin dat van een stofzuigerslang na met zijn individuele ronde stentringen die hem flexibiliteit geven en knikken voorkomen. Deformatie van de stentgraftpootjes tijdens de hartcyclus en tijdens de follow-up werd geëvalueerd met behulp van de data van een prospectieve observationele studie met ECG-gated CT-scans van 15 AAA-patiënten. Gedurende de follow-up-periode van twee jaar zagen we een toename van de curvatuur van de pootjes, verkorting van de pootjes en een overeenkomstige afname van de afstanden tussen opeenvolgende stentringen. Ondertussen bleef de door hartslag-geïnduceerde deformatie redelijk constant tijdens de follow-up met veranderingen gedurende de hartslag in curvatuur variërend tussen 1-2% van de waarde halverwege de hartcyclus en veranderingen in afstanden tussen de stent-ringen en lengte van het pootje van ca. 0,3%. Dankzij zijn flexibele ontwerp kan de Anaconda stentgraft worden geplaatst bij patiënten met een kronkelige

vasculaire anatomie die niet geschikt is voor andere EVAR-stentgrafts. Uit dit hoofdstuk kwam echter de hypothese naar voren dat dit ontwerp waarschijnlijk de keerzijde heeft dat het graftmateriaal naar binnen kan vouwen wanneer de afstanden tussen de individuele stentringen aanzienlijk afnemen als gevolg van toegenomen curvatuur en/of verkorting van de pootjes. Tussen deze plooien van het graftmateriaal kan het bloed stil gaan staan en/of een turbulente stroming krijgen, wat trombusformatie tot gevolg kan hebben en daarmee mee kan spelen in het verhoogde aantal pootocclusies dat gezien wordt bij dit specifieke type stentgraft. Dit fenomeen wordt ook wel het Concertinaeffect genoemd.

De hypothese van het Concertinaeffect in de pootjes van de Anaconda werd verder onder- zocht in **Hoofdstuk 4** door een cohort van 84 patiënten met een AAA dat was behandeld met een Anaconda stentgraft te evalueren. De resultaten toonden aan dat het risico op trombo-embolische events (pootocclusie en distale trombo-embolieën uit de stentgraft) na EVAR met de Anaconda stentgraft afneemt bij patiënten met meer circumferentiële verkalking van de arteria iliaca communis (CIA) en een sterkere afname van de curvatuur en tortuositeitsindex na EVAR. Deze bevindingen ondersteunen de hypothese dat het flexibele design van deze stentgraft als keerzijde het Concertinaeffect kan veroorzaken dat bijdraagt aan de ontwikkeling van trombo-embolische events. Op basis van dit onderzoek en met de intentie het aantal trombo-embolische events te verminderen, werd de gebruiksaanwijzing van de Anaconda bijgewerkt met het advies om de stentgraftpootjes gestrekt te plaatsen en zo overtollig graftmateriaal in het lumen van de pootjes te vermijden gezien het risico op trombusontwikkeling.

De meeste complicaties na FEVAR zijn gerelateerd aan de zij-stents in de viscerale zijtak- ken van de aorta, of aan de proximale sealing en fixatie van de main-body van de stentgraft- configuratie. De stentgraftdeformatie tijdens de hartcyclus en tijdens de follow-up van 19 gefenestreerde Anaconda's met V12 zij-stents bij patiënten met een complex AAA werd beschreven in **Hoofdstuk 5**. Hier werd beperkte deformatie waargenomen wat betreft de volgende variabelen: de hoek tussen het einde van de zij-stent en het natieve vat daarna, de curvatuur en de tortuositeitsindex. Dit suggereert dat deze FEVAR-configuraties als stabiel en duurzaam kunnen worden beschouwd. Desalniettemin, tijdens de follow-up namen de hoeken tussen de aorta en de zijtakken toe. Vooral de hoek tussen de nierarteriën en de aorta nam toe naar een loodrechte oriëntatie. Daarom is zorgvuldigheid geboden bij aanzienlijk toenemende hoeken tussen de aorta en haar zijtakken en andere geometrie- veranderingen, aangezien dit de ontwikkeling van zij-stentgerelateerde complicaties kan bevorderen. Deze geometrieveranderingen worden waarschijnlijk meer stroomafwaarts in de zijtakken gecompenseerd, met mogelijke verstoringen van de bloedstroming tot gevolg.

In **Hoofdstuk 6** werd de deformatie van de proximale sealing-ringen tijdens de hartcyclus en tijdens follow-up van zowel de standaard als de gefenestreerde Anaconda stentgrafts gekwantificeerd en vergeleken. Op alle follow-up-tijdstippen werd een beperkte pulsatiele expansie waargenomen, wat gunstig wordt geacht voor de duurzaamheid van de stent- graft. De pulsatiele verplaatsing, expansie en curvatuurverandering van de proximale sealing-ringen was echter niet gelijkmatig, maar juist minder aan de posterieure zijde van de aorta. Deze asymmetrische deformatie moet in acht genomen worden bij stentgraft- ontwikkeling en stentgraftkeuze om goede sealing en fixatie van de stentgraft te waar- borgen. Bovendien kan de in dit hoofdstuk beschreven methode ook helpen bij het identificeren van afwijkende lokale deformatiepatronen van de stentringen die kunnen wijzen op gebieden die risico lopen op stentmoeheid of toekomstige endolekkage als gevolg van onvoldoende sealing bij bijvoorbeeld lokale aortawandverzwakking.

In **Hoofdstuk 7** werd de door hartslag-geïnduceerde deformatie van het aorto-iliacale traject voor en na plaatsing van de Gore Excluder Iliac Branch Endoprosthesis (IBE) geëvalueerd. De IBE dempte de cardiale drukgolf langs het onderzochte aorto-iliacale traject. De beweging van de arteria iliaca interna (IIA) bleek echter te zijn toegenomen na plaatsing van de IBE. Het CIA-IIA-traject werd

postoperatief verkort en opgestrekt, waargenomen als een vermindering van curvatuur, lengte en tortuositeitsindex. De verminderde hartslag-geïnduceerde curvatuurverandering van het CIA-IIA-traject duidde op verstijving van het traject. Deze verstijving kan leiden tot een compliantie-mismatch tussen de gestentte en de niet-gestentte arteriën, wat zou kunnen leiden tot lokale bloedstromingsverstoringen die trombusvorming en andere complicaties kunnen veroorzaken.

Het postoperatieve gedrag van de IBE werd in **Hoofdstuk 8** vergeleken met dat van een stijver IBD, de Cook Zenith Bifurcated Iliacale Side (ZBIS). Deze vergelijking liet meer uitgesproken pulsatiele verplaatsing zien gedurende de hartcyclus in de IBE dan in de ZBIS over het hele CIA-IIA-traject, vooral in de cranio-caudale richting. Daarnaast bleek de IBE flexibeler en meer conformeerbaar te zijn dan de ZBIS. Dit kan worden verklaard door de self-expandable stents, zoals de speciale IIA-component van de IBE, die over het algemeen minder stijf en daarmee meer conformeerbaar zijn dan balloon-expandable stents, zoals de V12 stents die werden gebruikt als ZBIS IIA-component.

In **Hoofdstuk 9** werd een nieuw terrein verkend door de deformatie van de aortaboog en zijn zijtakken te onderzoeken na branched TEVAR (BTEVAR). De gepresenteerde casus betrof een patiënt met een aortabooganeurysma dat werd behandeld met BTEVAR en op- gevolgd met ECG-gated CT-scans. De pulsatiele diametrische expansie van de aortaboog nam in de loop van de tijd af, wat suggereert dat de aortaboog stijver werd. De verhoog- de stijfheid van de aortaboog na BTEVAR vermindert de windkesselfunctie van de aorta en verhoogt de weerstand voor het bloed om de aorta in te stromen. De continuerende afname van pulsatiele diametrische expansie tijdens de follow-up kan erop wijzen dat de hartfunctie afneemt als gevolg van de toegenomen aortale verstijving en cardiale belasting. Daarnaast werd bij deze patiënt na BTEVAR een toegenomen mismatch waargenomen van pulsatiele beweging aan het einde van zij-stents in de zijtakken van de aorta-boog. De uiteinden van de zij-stents vertoonden significant meer beweging dan dezelfde locaties preoperatief en dan de eerste bifurcatie van deze arteriën. Deze mismatch kan ertoe leiden dat ofwel de zij-stents langs de vaatwand schrapen ofwel de zij-stents bij elke hartslag aan de vaatwand “trekken”. Deze beide gevolgen kunnen leiden tot verhoogde pulsatiele wandspanning en daaruit voortvloeiende intima-schade die dan weer micro-embolieën kan veroorzaken welke de aanhoudende herseninfarcten na BTEVAR zouden kunnen verklaren. Daarom is een zorgvuldige selectie van de patiënten en conformeerbare (zij-) stentgrafts van cruciaal belang bij BTEVAR.

Afgezien van de stentgraftdeformatie tijdens de hartcyclus en de follow-up, kunnen andere factoren bijdragen aan de uitkomsten van EVAR-procedures. Een van deze factoren is de positie en houding van het menselijk lichaam. Het menselijk lichaam bevindt zich niet constant in gestrekte rugligging zoals tijdens de CT scan, maar neemt gedurende de dag voortdurend verschillende posities en houdingen aan die de positie en vorm van de aorta en stentgraft zouden kunnen beïnvloeden. De eerste stap bij het onderzoeken in hoeverre verschillende lichaamsposities en -houdingen invloed kunnen hebben op de duurzaamheid van EVAR behandelingen is het visualiseren van de aorta (en stentgraft) in deze posities en houdingen. Echter, uit de scoping review gepresenteerd in **Hoofdstuk 10** van dit proefschrift bleek dat dit slechts in beperkte mate is gedaan. Vooral met het toenemende aantal endovasculaire behandelingen van arteriële pathologieën zou het interessant zijn om de deformatie van de arteriën en stents te kwantificeren in verschillende lichaamshoudingen en -posities, zodat hiermee rekening kan worden gehouden bij de (planning van de) behandeling en de ontwikkeling van stents.

In conclusie, dit proefschrift laat de potentiële relatie zien tussen klinische uitkomsten en stentgraftdeformatie met behulp van gedetailleerde analyse van ECG-gated CT-scans. De bewegingspatronen en geometrische variabelen werden berekend voor verschillende soorten EVAR in de gehele aorta. De bevindingen kunnen worden vertaald naar de klinische praktijk en het ontwerp en de ontwikkeling van stentgrafts. Zo wordt nu geadviseerd om Anacondapootjes opgestrekt te plaatsen om het Concertinaeffect te voorkomen, zoals beschreven in de gebruiksaanwijzing, en is de

stijfheid van zij-stents voor FEVAR, IBD en BTEVAR een punt van discussie en verbetering voor zowel de behandelaars als de stentgraftfabrikanten. Daarnaast kunnen stentgrafts die voor hetzelfde doel zijn gemaakt verschillend in situ gedrag vertonen als gevolg van verschillen in anatomie en stent-graftontwerp. Dit benadrukt de relevantie van in vivo deformatieanalyse van de aorta en stentgrafts, welke ook van groot belang is voor nauwkeurige stress-strain-analyse, evaluatie van stentmoeheid en ontwerpverificatie, en daarom onderdeel zou moeten zijn van Conformité Européenne (CE, Europese conformiteit) en Food and Drug Administratie (FDA) goedkeuringsprocedures. Desalniettemin, om het succes en falen van EVAR-stentgrafts volledig te begrijpen, moet ook rekening worden gehouden met andere bijdragende factoren, zoals de ademhalingscyclus, lichaamspositie en -houding, en fysiologische en bio- chemische aspecten van het bloed en de arteriële wand.

POSITION-DEPENDENT VASCULAR IMAGING WITH TILTABLE MRI

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the degree of doctor at the University of Twente,
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on Friday the 1st of December 2023 at 12.45 hours

by

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Co-promotor:	Dr. Ir. F.F.J. Simonis

Samenvatting

Cardiovasculaire aandoeningen (CVD's) zijn een belangrijke wereldwijde oorzaak van overlijden, met meer dan 500 miljoen gevallen en 18 miljoen jaarlijkse sterfgevallen. Hoewel risicofactoren voornamelijk de bloedvaten van binnenuit beïnvloeden, spelen externe krachten ook een aanzienlijke rol bij de ontwikkeling en ernst van CVD, waarbij ze de fijne balans van het vasculaire systeem beïnvloeden. Het begrijpen van CVD's vereist een grondige verkenning van zowel interne als externe factoren die bijdragen aan hun ontwikkeling. Externe krachten die van invloed zijn op de lichaamshouding, zoals zwaartekracht, worden al lang erkend als invloedrijk voor het vasculaire systeem en de bloedcirculatie, maar diens implicaties voor diagnose en behandeling zijn onderbelicht gebleven. Door de invloed van deze lichaamshouding op CVD's te onderzoeken, willen we de cardiovasculaire geneeskunde verbeteren, de resultaten voor patiënten verbeteren en daarmee uiteindelijk de maatschappelijke lasten verminderen.

Kantelbare magnetic resonance imaging (MRI) is voornamelijk eerder toegepast in musculoskeletale beeldvorming, waarbij gekeken wordt naar de invloed van de zwaartekracht op gewrichts- en botstructuren. De mogelijke invloed ervan op andere lichaamsstructuren, waaronder het vasculaire systeem, is echter minder onderzocht. Slechts enkele studies hebben de respons van het vasculaire systeem op verschillende lichaamshoudingen onderzocht met behulp van kantelbare laagveld-MRI. Over het algemeen ontbreekt een uitgebreid overzicht van positieafhankelijke vasculaire beeldvorming, wat implicaties heeft voor het diagnosticeren en behandelen van cardiovasculaire aandoeningen en het begrijpen van vasculaire routes in verschillende lichaamshoudingen en posities. Dit proefschrift richt zich op positieafhankelijke vasculaire beeldvorming met behulp van laagveld-MRI om meer inzicht te verschaffen in dit onderbelichte gebied.

Het doel van dit proefschrift is om de toegevoegde waarde en haalbaarheid van positieafhankelijke vasculaire beeldvorming met kantelbare MRI aan te geven. Daarnaast beoogd dit proefschrift waardevolle suggesties te bieden over hoe dit relatief onbekende domein zich kan ontwikkelen naar succesvolle klinische implementaties.

Om een basis te leggen voor ons onderzoek, hebben we in **Hoofdstuk 2** een verkennend literatuuronderzoek uitgevoerd om te onderzoeken wat er momenteel is gedaan en wat er mogelijk is, en om kennishiaten te identificeren binnen het domein van positie- en houdingsafhankelijke vasculaire beeldvorming. Onze primaire focus lag op het begrijpen van de geometrische variaties die optreden in verschillende lichaamshoudingen en posities. De meerderheid van deze studies gebruikte echografie als hun beeldvormingsmodaliteit, met een nadruk op het perifere gebied, gevolgd door het hoofd- en nekgebied. Onze bevindingen lieten zien dat het veneuze systeem gevoeliger is voor houdingsveranderingen dan het arteriële systeem, wat werd gekenmerkt door een toename van de veneuze diameters onder het niveau van het hart bij overgang van liggende naar buikligging naar staande houdingen, en vice versa. Deze variaties werden voornamelijk toegeschreven aan positionele veranderingen (bijvoorbeeld zitten, rechtop staan, gekantelde posities) in plaats van houdingsaanpassingen (bijvoorbeeld ledematenbuiging, -strekking, hoofdrotatie). In ongeveer 20% van de studies werd MRI gebruikt. MRI was met name waardevol voor het beoordelen van complexere geometrische parameters zoals kromming en kronkeligheid ('tortuosity') vanwege zijn driedimensionale aard. De belangrijkste klinische implicaties van positionele veranderingen worden gevonden in diagnose en chirurgische planning, evenals stentplaatsing en follow-up na behandeling. Door deze kennishiaten te identificeren en aan te pakken, streven we ernaar bij te dragen aan de ontwikkeling van medische beeldvormingstechnieken en de verbetering van de patiëntenzorg in verschillende klinische scenario's.

De afhankelijkheid van de positie is herhaaldelijk aangetoond in het vasculaire domein. **Hoofdstuk 3** van dit proefschrift heeft als doel het begrip van geometrische variaties in de doorgankelijkheid ('patency') van de interne halsaders te verbeteren onder invloed van verschillende

lichaamshoudingshoeken. Hoewel deze informatie klinisch relevant zou kunnen zijn voor patiënten met beperkte veneuze drainage, zoals die met chronische cerebrospinale veneuze insufficiëntie, werd het onderzoek uitgevoerd met gezonde vrijwilligers. Het primaire doel was om de bruikbaarheid van kantelbare laagveld-MRI te laten zien bij het beoordelen van de geometrie van de halsaders en alternatieve vasculaire routes die duidelijk worden in meer rechtopstaande posities. Om dit te bereiken, ondergingen vijftien gezonde vrijwilligers kantelbare MRI-scans bij verschillende hellingshoeken. De beoordeling van de vaten toonde de haalbaarheid van onze techniek in het verstrekken van waardevolle informatie. We observeerden een toenemende prevalentie van dichtgevallen vaten bij grotere hellingshoeken. Bovendien was er een afname van de gemiddelde diameter van niet-dichtgevallen vaten naarmate de hellingshoeken toenamen, zowel voor de linker als de rechter interne halsader. Bovendien stelde deze studie ons in staat om in meer detail te onderzoeken dat de linker interne halsader veel eerder neigde tot dichtvallen dan zijn rechter tegenhanger. Dit was mogelijk door de inclusie van meerdere hellingshoeken en langere vaat trajecten in ons onderzoek, in tegenstelling tot eerder onderzoek met echografie. Deze bevindingen zijn waardevol voor patiënten met verminderde veneuze terugkeer naar het hart, aangezien verbeterde 3D-visualisatietechnieken onder variërende hellingshoeken hun diagnose en behandeling kunnen verbeteren.

Binnen het arteriële systeem hebben we een klinische studie uitgevoerd naar complicaties na endovasculaire aneurysmaverwijdering. Ondanks behandeling van abdominale aorta-aneurysmata ervaren sommige patiënten complicaties, waaronder aanhoudende lekkages (‘endoleaks’) rondom de geïmplanteerde stents, ook wel endografts genoemd. Er kan worden gedacht dat deze complicaties mogelijk worden beïnvloed door de lichaamshouding. Hiervoor hebben we een klinisch onderzoek opgezet met patiënten die een endograft hadden gekregen voor abdominale aneurysma’s. **Hoofdstuk 4** heeft tot doel de potentiële voordelen te evalueren van het gebruik van kantelbare MRI voor het onderzoek naar stentlekkages, met name lekkages welke eerder onverklaarbaar waren en werden vermoed als afhankelijk van de houding. We hebben tien patiënten geïncludeerd die eerder endovasculaire behandeling hebben gehad en ze met een kantelbare MRI-scanner gescand in zowel de liggende als rechtopstaande houdingen. Vervolgens hebben we de resultaten van beide MRI-standen vergeleken met die van de gouden standaard diagnostiek, computed tomography angiografie (CTA). In deze studie hebben we aangetoond hoe de beeldkwaliteit in zowel rechtopstaande als liggende MRI werd vergeleken met CTA, en hebben we de specifieke aspecten geïdentificeerd waarin CTA beter presteerde dan MRI. Bovendien stond MRI toe dat anatomische kenmerken en endograft-kenmerken met een nauwkeurigheid van ongeveer 6-7 mm werden beoordeeld. Met dit niveau van nauwkeurigheid zou optimalisatie van scanacquisitie technieken en beeldkwaliteit nodig zijn voordat eventuele mogelijke vervormingen kunnen worden gedetecteerd. Wat betreft de detectie van endoleaks waren we in staat om CTA-bevestigde endoleaks in de helft van de gevallen te bevestigen. Bovendien bracht MRI extra bevindingen aan het licht bij één patiënt, die potentieel klinisch relevant waren en nader onderzoek rechtvaardigden. Hoewel onze resultaten beperkte aanvullende waarde van rechtopstaande MRI voor endoleak detectie suggereerden, identificeerden we specifieke scenario’s waarin rechtopstaande MRI voordelen zou kunnen bieden. Het is echter essentieel om de belangrijkste beperkingen van laagveld-MRI aan te pakken voordat patiënten met vermoedelijke stentlekkages volledig kunnen profiteren van deze innovatieve techniek. De haalbaarheid van deze aanpak werd onderzocht in dit proefschrift en opent de weg voor toekomstige ontwikkelingen in vasculaire beeldvorming.

In dit proefschrift hebben we verschillende verbeterpunten geïdentificeerd voor het gebruik van laagveld MRI-technieken in meer klinisch georiënteerde studies. Om deze verbeteringen te adresseren en het contrast binnen bloedvaten te verbeteren, hebben we een fundamentele studie uitgevoerd gericht op de voordelen van een nieuw contrastmiddel. Het is algemeen bekend dat het gedrag van contrastmiddelen in MRI nauw verband houdt met de gebruikte magnetische veldsterkte. Daarom kunnen alternatieve contrastmiddelen voor de veelgebruikte gadolinium-gebaseerde

middelen in laagveld-MRI verbeteringen bieden wat betreft beeldcontrast. In **Hoofdstuk 5** zijn we begonnen met een fantoom- en simulatiestudie om de geschiktheid van een gadolinium-gebaseerd contrastmiddel te beoordelen in vergelijking met een superparamagnetisch ijzeroxide middel (ferumoxytol) bij een veldsterkte van 0.25T. Ons onderzoek toonde aan dat ferumoxytol een vergelijkbare signaalversterking kon produceren, maar bij lagere concentraties. De klinische toepassing van een dergelijk contrastmiddel bij de juiste dosering in laagveld-MRI heeft het potentieel om vasculaire beeldvorming op een veiligere en efficiëntere manier te verbeteren. Dit onderzoek vertegenwoordigt een stap voorwaarts in het optimaliseren van het gebruik van laagveld MRI-technologie voor klinische toepassingen, wat de beeldkwaliteit voor vasculaire studies zal verbeteren.

Samenvattend lijkt de toekomst van kantelbare MRI veelbelovend, hoewel de klinische toepassing van positie-afhankelijke beeldvorming nog in de beginfase verkeert. Hoewel kantelbare MRI potentieel klinische voordelen en haalbaarheid heeft aangetoond, moeten verschillende beperkingen worden aangepakt voordat het een betrouwbare beeldvormingsmodaliteit kan worden in vasculaire gezondheidszorg. Ondanks de beperkingen die gepaard gaan met laagveld-MRI, biedt dit werk een basis voor het begrijpen van positioneel afhankelijke vasculaire verschijnselen en opent het de weg voor verder onderzoek en mogelijke verbeteringen in de patiëntenzorg.

Kindergeneeskunde

EHEALTH IN PEDIATRIC ASTHMA CARE
FROM SMART HOME-MONITORING TO IMPLEMENTING A NEW CARE STANDARD

ter verkrijging van
de graad van doctor aan de Universiteit Twente, op gezag van de rector magnificus,
prof. dr. ir. A. Veldkamp,
volgens besluit van het College voor Promoties in het openbaar te verdedigen
op vrijdag 21 april 2023 om 14.45 uur

door

Mattiènne Ricard van der Kamp
geboren op 11 maart 1992
in Kampen, Nederland

Promotoren:	Prof. Dr. Ir. M. Tabak
	Prof. Dr. Ir. H.J. Hermens
Co-promotor:	Dr. B.J. Thio

Samenvatting
Astma bij kinderen is een hoog prevalente chronische aandoening die het fysieke-, sociale- en emotionele welzijn kan belemmeren. Regelmatige monitoring van astma bij kinderen is nodig om verslechtering van de ziekte te voorkomen en de kwaliteit van leven te verbeteren. De huidige organisatie van de kinderastmazorg met electieve polikliniekbezoeken lijkt echter slecht aan te sluiten bij de episodische aard van astma. eHealth-technologie biedt mogelijkheden om objectiever te monitoren wanneer symptomen zich daadwerkelijk in het dagelijks leven voordoen, waardoor een adequate en tijdige behandeling mogelijk is. Literatuur over de inzet van eHealth bij kinderastma heeft 1) een grote heterogeniteit in studie-eindpunten en ontwerpen, 2) richt zich vaak op specifieke enkelvoudige parametermonitoring, terwijl astma een heterogene ziekte is en 3) is vaak niet specifiek gericht op de kinderpopulatie, waardoor opname in klinische richtlijnen vooralsnog zeer beperkt is. Dit proefschrift focust zich daarom op de validatie, implementatie en evaluatie van objectieve thuismonitoring als onderdeel van eHealth-ondersteunde kinderastmazorg.

Deel I richt zich op de identificatie van verschillende (fysiologische) parameters voor thuismonitoring van astma. Om overzicht te krijgen over de huidige stand van zaken, hebben we een scoping review uitgevoerd naar eHealth thuismonitoringstechnologieën binnen de kinderastma (**hoofdstuk 2**). Deze review toont de afgelopen jaren een versnelde toename in het aantal eHealth-onderzoeken. Verschillende thuismonitoringdomeinen (luchtkwaliteit, ontstekingsmarkers van de luchtwegen, longfunctie, activiteit, slaap, audiovisuele monitoring, andere fysiologische metingen, vragenlijsten, medicatie-monitoring en digitale omgeving) werden geïdentificeerd en de ontwikkeling, validatie en interventiestudies in deze domeinen zijn beschreven. Ondanks de heterogeniteit in onderzoeksopzetten en uitkomstmaten lijken interventiestudies niet-inferioriteit en mogelijke superioriteit van eHealth-monitoring en behandeling bij kinderastma aan te geven. Deze review toont slechts een beperkt aantal studies naar multiparameter monitoringstrategieën. Toekomstig onderzoek zou zich kunnen richten op het evalueren van ziekenhuis diagnostiek die potentieel relevant is voor thuis-monitoring.

Hoofdstuk 3 richt zich op zo'n potentiële thuismonitoringparameter, door middel van het onderzoek naar de diagnostische waarde van diafragma elektromyografie (EMG) bij kinderen met astma. Oppervlakte EMG is een non-invasieve meting die de belasting van de respiratoire fysiologie weerspiegelt. Voor deze studie werden EMG-metingen uitgevoerd voor elke spirometrietest bij astmatische kinderen die een inspanningsprovocatietest ondergingen. De studie toonde een sterk verband tussen EMG-parameters (piekamplitude en oppervlakte onder de curve) en longfunctie. Dit suggereert dat EMG een alternatief kan zijn voor wanneer spirometrie niet haalbaar is. Fysieke activiteit is een ander enkelvoudig monitoringsdomein dat relevant kan zijn voor het monitoren van (in)directe gedragsaanpassing aan astma. **Hoofdstuk 4** onderzocht de patronen van dagelijkse fysieke activiteit, objectief beoordeeld met accelerometrie, bij astmatische kinderen met breakthrough inspanningsastma, klassieke inspanningsastma en zonder inspanningsastma. Deze studie toont aan dat astmatische kinderen met inspanningsastma andere activiteitspatronen hebben dan kinderen zonder inspanningsastma. Het meest opvallend hierbij zijn de kinderen met breakthrough inspanningsastma die minder, kortere en minder intense fysieke activiteiten lieten zien in vergelijking met kinderen zonder inspanningsastma.

Naar aanleiding van de behoefte voor multiparameter astma thuismonitoringstrategieën, onderzocht **hoofdstuk 5** of de astma controle nauwkeurig kan worden vastgesteld door middel van een twee weken durende thuismonitoring. Dit gebeurt middels een fysieke activiteiten meter, een handzame spirometer, slimme inhalatoren en een draagbare elektrocardiografiesensor. De variatie in longfunctie, de tijd van opstaan, het aantal gebruiken van luchtwegverwijderaars en de hersteltijd van de ademhalingsfrequentie na inspanning onderscheidden de gecontroleerde en ongecontroleerde astmagroep significant binnen de univariate analyse. Deze studie toont bovendien aan dat de combinatie van deze parameters 89% van de ongecontroleerde astmatische kinderen nauwkeurig kan

identificeren. Dit laat zien dat multiparameter monitoring potentie heeft voor de evaluatie van de kinderastmacontrole thuis.

Naast de objectieve fysiologische monitoring van astma, evalueert **hoofdstuk 6** de Visuele Analoge Schaal (VAS) voor waargenomen benauwdheid als een hulpmiddel om inspanningsastma te detecteren bij kinderen met astma. Deze studie toonde aan dat een gerapporteerd verschil in VAS-score van ≥3 gecombineerd met een lage astmacontrole- test (C)-ACT-score, zeer effectief inspanningsastma kan detecteren (sensitiviteit van 97%) en inspanningsastma bij een negatief testresultaat kan uitsluiten (negatieve voorspellende waarde 96%). Door zowel de waargenomen benauwdheid met de VAS-score als ook de objectieve longfunctie te meten, ontstaat een potentieel (thuis)hulpmiddel dat symptoomperceptie kan weergeven bij astmatische kinderen.

Deel II van dit proefschrift richt zich op de toepassing van bovenstaande kennis in de gezondheidszorg en de evaluatie van een pragmatische exploratieve eHealth-studie in de dagelijkse praktijk (**hoofdstuk 7**). Het doel van deze studie was het onderzoeken van de technische- en klinische haalbaarheid, waaronder een verkenning van de effectiviteit en efficiëntie binnen een matige tot ernstige astmapopulatie. Er werd een eHealth-programma van zes maanden aangeboden, waarbij communicatie op afstand met zorgprofessionals en multiparameter thuismonitoring werden gecombineerd. Wat betreft de technische haalbaarheid scoorde de eHealth-technologie een goede gebruiksvriendelijkheidsscore van 78 op de System Usability Scale (SUS) en een goede technologieacceptatie van 70, op een schaal van 1 tot 100. 75% van de kinderen en hun ouders gaven aan dat eHealth-zorg hen hielp om het astma tijdens de eHealth zorg onder controle te houden. Zorgprofessionals gaven aan dat thuismetingen en real-time communicatie hen in staat stelden om veilige en gefundeerde medische beslissingen te nemen tijdens symptoommanifestaties. eHealth-zorg leidde tot een 80% bruto-reductie in medisch zorgverbruik, een 9% stijging in astmacontrole, een 25% stijging in zelfmanagement en een 20% verbetering van de therapietrouw in vergelijking met historische controle. Deze resultaten suggereren een hoge haalbaarheid voor het gebruik van eHealth kinderastmazorg en vraagt om herhaling en validering met een gerandomiseerde studie.

Hoofdstuk 8 beschrijft het protocol voor zo'n prospectieve gerandomiseerde studie om vooral de effectiviteit van een eHealth-interventie, bestaande uit thuismonitoring en teleconsultatie, te onderzoeken op het verminderen van medisch zorggebruik. Daarnaast streeft deze studie ernaar de toekomstige eHealth kinderastmazorg te verbeteren door inzichten te verkrijgen uit thuismonitoringsgegevens (medicijngebruik, longfunctie, zuurstofsaturatie, slaap, nachtelijke hart- en ademhalingsfrequentie, nachtelijk hoesten en piepen en de luchtkwaliteit in de slaapkamer). Bovendien zal de follow-up periode van drie maanden toelaten om te onderzoeken of effect kan aanhouden wanneer eHealth wordt gestaakt. Hierdoor kan unieke informatie verkregen worden over de mogelijke lange termijn voordelen van eHealth kinderastmazorg. Deze studie zal bijdragen aan de bestaande kennis over de effectiviteit van eHealth kinderastma-interventies. Bovendien kunnen de exploratieve thuismonitoringsgegevens bijdragen aan een verbeterde identificatie van vroege tekenen van astmaverslechtering.

De jaren 2020 en 2021 zullen de geschiedenis in gaan als de periode van de COVID-19 pandemie. **Hoofdstuk 9** rapporteert onze perspectieven op de nieuwe aanpak voor de klinische-, organisatorische- en wetenschappelijke aspecten van het gebruik van eHealth technologie in kinderastmazorg ten tijde van COVID-19. Het geeft tevens ook een casus van een acute astma-exacerbatie, gevolgd via eHealth zorg, mogelijk veroorzaakt door een COVID-19 infectie. Deze casus illustreerde dat technologie ondersteunde eHealth het mogelijk maakt om veilige acute zorg op afstand te faciliteren en het gebruik van vernevelingen en orale steroïden te voorkomen. Bovendien bleek dat de COVID-19 crisis een grote impact heeft gehad op het gehele zorgsysteem en een hoge intrinsieke motivatie heeft veroorzaakt voor zorg op afstand. Dit heeft geleid tot de versnelde introductie van thuisdiagnostiek en monitoringsmethoden om in contact te blijven met patiënten op

afstand. Een belangrijke les die is geleerd uit de COVID-19 crisis is dat we relevante eHealth-elementen wereldwijd kunnen gebruiken als bouwstenen om eigen eHealth-programma's aan te passen aan specifieke zorgomgevingen.

Hoofdstuk 10 gaat in detail in op de belangrijkste bevindingen van dit proefschrift, waarbij tevens de uitdagingen en aanbevelingen voor klinische implementatie worden besproken. In het kort, benadrukt dit proefschrift de hoge potentie van objectieve thuismonitoring binnen de toepassing van eHealth kinderastmazorg. Het combineren van thuismonitoringparameters lijkt de nauwkeurige beoordeling van astmacontrole te verbeteren, terwijl modificeerbare risicofactoren en persoonlijke knelpunten van het astmamanagement worden geïdentificeerd. De implementatie van eHealth zorg, waarbij multiparameter thuismonitoring en online communicatie worden gecombineerd, blijkt een positief effect te hebben op de efficiëntie en effectiviteit van kinderastmazorg, wat verdere stappen in onderzoek en implementatie rechtvaardigt. De vervolgstappen zouden zich kunnen richten op het ontwikkelen van multiparameter monitoringstrategieën over de tijd, het bevorderen van opname in klinische richtlijnen, het overwinnen van huidige implementatiebelemmeringen en het mogelijk maken van digitale samenwerking van zorgprofessionals.

Anesthesie

1. Is Continuous Intraoperative Monitoring of Mean Arterial Pressure as Good as the Hypotension Prediction Index Algorithm?: Research Letter
Mulder MP, Harmannij-Markusse M, Donker DW, Fresiello L, Potters JW.

Gepubliceerd: Anesthesiology. 2023;138(6):657-8.
Impact factor: 8.8 ; Q1

Totale impact factor: 8.8
Gemiddelde impact factor: 8.8

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 8.8
Gemiddelde impact factor: 8.8

Gynaecologie

1. Long-term outcomes of switching to gonadotrophins versus continuing with clomiphene citrate, with or without intrauterine insemination, in women with normogonadotropic anovulation and clomiphene failure: follow-up study of a factorial randomized clinical trial
Bordewijk EM, Jannink TI, Weiss NS, de Vries T, Nahuis M, Hoek A, Goddijn M, Mol BW, van Wely M, M-ovin study group: Hoozemans DA.

Study question: What are the long-term outcomes after allocation to use of gonadotrophins versus clomiphene citrate (CC) with or without IUI in women with normogonadotropic anovulation and clomiphene failure?
Summary answer: About four in five women with normogonadotropic anovulation and CC failure had a live birth, with no evidence of a difference in pregnancy outcomes between the allocated groups.
What is known already: CC has long been used as first line treatment for ovulation induction in women with normogonadotropic anovulation. Between 2009 and 2015, a two-by-two factorial multicentre randomized clinical trial in 666 women with normogonadotropic anovulation and six cycles of CC failure was performed (M-ovin trial). This study compared a switch to gonadotrophins with continued treatment with CC for another six cycles, with or without IUI within 8 months. Switching to gonadotrophins increased the chance of conception leading to live birth by 11% over continued treatment with CC after six failed ovulatory cycles, at a cost of €15 258 per additional live birth. The addition of IUI did not significantly increase live birth rates.
Study design, size, duration: In order to investigate the long-term outcomes of switching to gonadotrophins versus continuing treatment with CC, and undergoing IUI versus continuing with intercourse, we conducted a follow-up study. The study population comprised all women who participated in the M-ovin trial.
Participants/materials, setting, methods: The participating women were asked to complete a web-based questionnaire. The primary outcome of this study was cumulative live birth. Secondary outcomes included clinical pregnancies, multiple pregnancies, miscarriage, stillbirth, ectopic pregnancy, fertility treatments, neonatal outcomes and pregnancy complications.
Main results and the role of chance: We approached 564 women (85%), of whom 374 (66%) responded (184 allocated to gonadotrophins; 190 to CC). After a median follow-up time of 8 years, 154 women in the gonadotrophin group had a live birth (83.7%) versus 150 women in the CC group (78.9%) (relative risk (RR) 1.06, 95% CI 0.96-1.17). A second live birth occurred in 85 of 184 women (49.0%) in the gonadotrophin group and in 85 of 190 women (44.7%) in the CC group (RR 1.03, 95% CI 0.83-1.29). Women allocated to gonadotrophins had a third live birth in 6 of 184 women (3.3%) and women allocated to CC had a third live birth in 14 of 190 women (7.4%). There were respectively 12 and 11 twins in the gonadotrophin and CC groups. The use of fertility treatments in the follow-up period was comparable between both groups. In the IUI group, a first live birth occurred in 158 of 192 women (82.3%) and while in the intercourse group, 146 of 182 women (80.2%) reached at least one live birth (RR: 1.03 95% CI 0.93-1.13; 2.13%, 95% CI -5.95, 10.21).
Limitations, reasons for caution: We have complete follow-up results for 57% of the women.There were 185 women who did not respond to the questionnaire, while 102 women had not been approached due to missing contact details. Five women had not started the original trial.

Wider implications of the findings: Women with normogonadotropic anovulation and CC failure have a high chance of reaching at least one live birth. In terms of pregnancy rates, the long-term differences between initially switching to gonadotrophins are small compared to continuing treatment with CC.
Study funding/competing interest(s): The original study received funding from the Dutch Organization for Health Research and Development (ZonMw number: 80-82310-97-12067). A.H. reports consultancy for development and implementation of a lifestyle App, MyFertiCoach, developed by Ferring Pharmaceutical Company. M.G. receives unrestricted grants for scientific research and education from Ferring, Merck and Guerbet. B.W.M. is supported by an NHMRC Investigatorgrant (GNT1176437). B.W.M. reports consultancy for ObsEva and Merck and travel support from Merck. All other authors have nothing to declare.
Trial registration number: This follow-up study was registered in the OSF Register, https://osf.io/pf24m. The original M-ovin trial was registered in the Netherlands Trial Register, number NTR1449.

Gepubliceerd: Hum Reprod. 2023;38(3):421-9.
Impact factor: 6.1 ; Q1

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2. Long-term consequences of juvenile vulvar lichen sclerosus: A cohort study of adults with a histologically confirmed diagnosis in childhood or adolescence
Morrel B, van der Avoort IAM, Ewing-Graham PC, Damman J, Schappin R, van Zeijl KN, Voorham QJM, Ten Kate-Booij MJ, Burger CW, Pasmans S, Steering Group-JVLS: Maassen MS.

Introduction: Vulvar lichen sclerosus (VLS) occurs in at least one in 900 girls. There is limited knowledge as to what extent the disease persists in adulthood and what the repercussions in adulthood may be. The aim of this study is to evaluate the long-term consequences of VLS diagnosed in childhood or adolescence.
Material and methods: The population of females histologically diagnosed with VLS in childhood or adolescence in the Netherlands between 1991 and 2015 was identified through the national pathology database. Histological specimens were retrieved and re-evaluated. Potential participants for whom the diagnosis was reconfirmed and who are now adults, were then traced and surveyed. Descriptive statistics were calculated and compared with the literature. Main outcome measures are the demographics of the cohort, their scores on standardized quality of life (QoL) and sexuality questionnaires and answers to additional questions regarding patients' experience with the disease. The questionnaires used were the Dermatology Life Quality Index (DLQI), the Skindex-29, the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale-Revised (FSDS-R). Secondary outcome measures include obstetric history and histological features found in the original tissue specimens.
Results: A total of 81 women participated, median age 29.0 years, median follow-up from childhood diagnosis 19.5 years. Both QoL and sexuality were somewhat affected in 51.9% of cases. Less than half (45%) reported having regular check-ups. Forty-five (56%) reported symptoms within the past year; of those with symptoms, 14 (31%) were not under surveillance. Cesarean section rate (14.5%) was comparable to the general population, and there were more high-grade obstetric anal sphincter injuries with vaginal deliveries than expected. Sixteen respondents (20%) were not aware of the childhood diagnosis prior to this study.
Conclusions: Symptoms due to VLS are reported by most adults diagnosed as juveniles. QoL and sexuality are affected and correlate to recent symptoms. VLS as a juvenile does not preclude a vaginal delivery. Women diagnosed with VLS in childhood or adolescence are often lost to follow-up.

Gepubliceerd: Acta Obstet Gynecol Scand. 2023;102(11):1469-78.
Impact factor: 4.3 ; Q1

3. Cytoreductive Surgery with the PlasmaJet Improved Quality-of-Life for Advanced Stage Ovarian Cancer Patients
Nieuwenhuyzen-de Boer GM, Aamran H, van den Berg CB, Willemsen S, Piek JMJ, Reesink-Peters N, Maliepaard M, van Doorn HC, Polinder S, van Beekhuizen HJ.

Background: Knowledge of quality-of-life after cytoreductive surgery is important to counsel patients with advanced-stage epithelial ovarian cancer prior to surgery. The aim of this study was to determine whether the use of the PlasmaJet Surgical device during cytoreductive surgery has an effect on the quality-of-life of patients with advanced epithelial ovarian cancer.
Methods: Data included in this prospective observational study were derived from the PlaComOv study, in which patients with advanced epithelial ovarian cancer were randomly assigned to have cytoreductive surgery with or without adjuvant use of the PlasmaJet. Quality-of-life was measured before surgery and one, six, 12, and 24 months after surgery with three questionnaires: the EORTC QLQ-C30, QLQ-OV28, and EQ-5D-5L.
Results: Between 2018 and 2020, 326 patients were enrolled in the trial. The overall response rate was high, with the lowest response rate at 24 months of 77%. At 6 months, quality-of-life was higher in the intervention group (95%CI 0.009; 0.081, p = 0.045). At 12 months, quality-of-life was higher in the intervention group with fewer symptoms of fatigue, appetite loss, and diarrhea (95%CI 0.6; 10,0, p = 0.027); similarly, patients in the intervention group reported a better body image (95%CI -14.2; -3.0, p = 0.003) and a higher score on the visual analog scale (95%CI 1.99; 11.15, p = 0.005). At 24 months postoperatively, no further difference was found between the two groups except for pain (95%CI -12.9; -0.8, p = 0.027) and body image (95%CI -13.808; -0.733, p = 0.029). A higher quality-of-life in the intervention group was partially explained by the mediator 'surgery outcome'.
Conclusions: This study demonstrated knowledge of patients' quality-of-life until two years after cytoreductive surgery. The use of the PlasmaJet Surgical device during cytoreductive surgery leads to a higher quality-of-life than conventional surgery with electrocoagulation alone. Even after adjustment for the mediator of surgical outcome, a higher quality-of-life was seen in patients who had surgery with the use of the PlasmaJet device.

Gepubliceerd: Cancers (Basel). 2023;15(15).
Impact factor: 5.2 ; Q2

Totale impact factor: 15.6
Gemiddelde impact factor: 5.2

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

Heelkunde

1. Nationwide Outcomes of Octogenarians Following Open or Endovascular Management After Ruptured Abdominal Aortic Aneurysms

Alberga AJ, de Bruin JL, Bastos Gonçalves F, Karthaus EG, Wilschut JA, van Herwaarden JA, Wever JJ, Verhagen HJM, Collaboration With the Dutch Society of Vascular Surgery*, the Steering Committee of the Dutch Surgical Aneurysm Audit and the Dutch Institute for Clinical Auditing: Beuk RJ, Geelkerken RH, Meerwaldt R, Menting TP, Willigendael EM.

Purpose: Octogenarians are known to have less-favorable outcomes following ruptured abdominal aortic aneurysm (rAAA) repair compared with their younger counterparts. Accurate information regarding perioperative outcomes following rAAA-repair is important to evaluate current treatment practice. The aim of this study was to evaluate perioperative outcomes of octogenarians and to identify factors associated with mortality and major complications after open surgical repair (OSR) or endovascular aneurysm repair (EVAR) of a rAAA using nationwide, real-world, contemporary data.
Methods: All patients that underwent EVAR or OSR of an infrarenal or juxtarenal rAAA between January 1, 2013, and December 31, 2018, were prospectively registered in the Dutch Surgical Aneurysm Audit (DSAA) and included in this study. The primary outcome was the comparison of perioperative outcomes of octogenarians versus non-octogenarians, including adjustment for confounders. Secondary outcomes were the identification of factors associated with mortality and major complications in octogenarians.
Results: The study included 2879 patients, of which 1146 were treated by EVAR (382 octogenarians, 33%) and 1733 were treated by OSR (410 octogenarians, 24%). Perioperative mortality of octogenarians following EVAR was 37.2% versus 14.8% in non-octogenarians (adjusted OR=2.9, 95% CI=2.8-3.0) and 50.0% versus 29.4% following OSR (adjusted OR=2.2, 95% CI=2.2-2.3). Major complication rates of octogenarians were 55.4% versus 31.8% in non-octogenarians following EVAR (OR=2.7, 95% CI=2.1-3.4), and 68% versus 49% following OSR (OR=2.2, 95% CI=1.8-2.8). Following EVAR, 30.6% of the octogenarians had an uncomplicated perioperative course (UPC) versus 49.5% in non-octogenarians (OR=0.5, 95% CI=0.4-0.6), while following OSR, UPC rates were 20.7% in octogenarians versus 32.6% in non-octogenarians (OR=0.5, 95% CI=0.4-0.7). Cardiac or pulmonary comorbidity and loss of consciousness were associated with mortality and major complications in octogenarians. Interestingly, female octogenarians had lower mortality rates following EVAR than male octogenarians (adjusted OR=0.7, 95% CI=0.6-0.8).
Conclusion: Based on this nationwide study with real-world registry data, mortality rates of octogenarians following ruptured AAA-repair were high, especially after OSR. However, a substantial proportion of these octogenarians following OSR and EVAR had an uneventful recovery. Known preoperative factors do influence perioperative outcomes and reflect current treatment practice.

Gepubliceerd: J Endovasc Ther. 2023;30(3):419-32.
Impact factor: 2.6 ; Q2

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2. Oncological Safety and Potential Cost Savings of Routine vs Selective Histopathological Examination After Appendectomy: Results of the Multicenter, Prospective, Cross-Sectional FANCY Study

Bastiaenen VP, de Jonge J, Corten B, de Savornin Lohman EAJ, Kraima AC, Swank HA, van Vliet JLP, van Acker GJD, van Geloven AAW, In 't Hof KH, Koens L, de Reuver PR, van Rossem CC, Slooter GD, Tanis PJ, Terpstra V, Dijkgraaf MGW, Bemelman WA, Dutch Snapshot Research Group: van Duyn EB.

Objective: To investigate the oncological safety and potential cost savings of selective histopathological examination after appendectomy.

Background: The necessity of routine histopathological examination after appendectomy has been questioned, but prospective studies investigating the safety of a selective policy are lacking.
Methods: In this multicenter, prospective, cross-sectional study, inspection and palpation of the (meso)appendix was performed by the surgeon in patients with suspected appendicitis. The surgeon's opinion on additional value of histopathological examination was reported before sending all specimens to the pathologist. Main outcomes were the number of hypothetically missed appendiceal neoplasms with clinical consequences benefiting the patient (upper limit two-sided 95% confidence interval below 3:1000 considered oncologically safe) and potential cost savings after selective histopathological examination.
Results: Seven thousand three hundred thirty-nine patients were included. After a selective policy, 4966/7339 (67.7%) specimens would have been refrained from histopathological examination. Appendiceal neoplasms with clinical consequences would have been missed in 22/4966 patients. In 5/22, residual disease was completely resected during additional surgery. Hence, an appendiceal neoplasm with clinical consequences benefiting the patient would have been missed in 1.01:1000 patients (upper limit 95% confidence interval 1.61:1000). In contrast, twice as many patients (10/22) would not have been exposed to potential harm due to re-resections without clear benefit, whereas consequences were neither beneficial nor harmful in the remaining seven. Estimated cost savings established by replacing routine for selective histopathological examination were €725,400 per 10,000 patients.
Conclusions: Selective histopathological examination after appendectomy for suspected appendicitis is oncologically safe and will likely result in a reduction of pathologists' workload, less costs, and fewer re-resections without clear benefit.

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Impact Factor: 10.1; Q1

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3. The Diagnostic Value of Biomarkers in Acute Mesenteric Ischaemia Is Insufficiently Substantiated: A Systematic Review
Blauw JTM, Metz FM, Nuzzo A, van Etten-Jamaludin FS, Brusse-Keiser M, Boermeester MA, Peppelenbosch M, Geelkerken RH.

Objective: There is an urgent need for accurate biomarkers to support timely diagnosis of acute mesenteric ischaemia (AMI) and thereby improve clinical outcomes. With this systematic review, the aim was to substantiate the potential diagnostic value of biomarkers for arterial occlusive AMI.
Data sources: The Pubmed, Embase, and the Cochrane Library electronic databases were searched.
Review methods: A systematic review of the literature has been conducted to define the potential diagnostic value of biomarkers for arterial occlusive AMI. All studies including ≥ 10 patients describing biomarkers for macrovascular occlusive AMI between 1950 and 17 February 2023 were identified within the Pubmed, Embase, and the Cochrane Library electronic databases. There were no restrictions to any particular study design, but letters and editorials were excluded. The QUADAS-2 tool was used for the critical appraisal of quality. The study protocol was registered on Prospero (CRD42021254970).
Results: Fifty of 4334 studies were eligible for inclusion in this review. Ninety per cent of studies were of low quality. A total of 60 biomarkers were identified, with 24 in two or more studies and 15 in five or more studies. There was variation in reported units, normal range, and cut off values. Meta-analysis was not possible due to study heterogeneity. Biomarkers currently recommended by the European Journal of Vascular and Endovascular Surgery, European Society for Trauma and Emergency Surgery 2016, and World Society of Emergency Surgery 2017 guidelines also had heterogeneous low quality data for use in the diagnosis of AMI.
Conclusion: This systematic review demonstrates high heterogeneity and low quality of the available evidence on biomarkers for arterial occlusive AMI. No clinical conclusions can be drawn on a

biomarker or combination of biomarkers for patients suspected of arterial occlusive AMI. Restraint is advised when rejecting or determining AMI solely based on biomarkers.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2023.
Impact factor: 5.7 ; Q1

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4. Prophylactic Mesh Placement During Formation of an End-colostomy: Long-term Randomized Controlled Trial on Effectiveness and Safety
Brandsma HT, Hansson BM, Aufenacker TJ, de Jong N, KC VE, Mahabier C, Donders R, Steenvoorde P, de Vries Reilingh TS, Leendert van Westreenen H, Wiezer MJ, de Wilt JHW, Rovers M, Rosman C.

Objective: The aim of this study was to determine if prophylactic mesh placement is an effective, safe, and cost-effective procedure to prevent parastomal hernia (PSH) formation in the long term.
Background: A PSH is the most frequent complication after stoma formation. Prophylactic placement of a mesh has been suggested to prevent PSH, but long-term evidence to support this approach is scarce.
Methods: In this multicentre superiority trial patients undergoing the formation of a permanent colostomy were randomly assigned to either retromuscular polypropylene mesh reinforcement or conventional colostomy formation. Primary endpoint was the incidence of a PSH after 5 years. Secondary endpoints were morbidity, mortality, quality of life, and cost-effectiveness.
Results: A total of 150 patients were randomly assigned to the mesh group (n = 72) or nonmesh group (n = 78). For the long-term follow-up, 113 patients were analyzed, and 37 patients were lost to follow-up. After a median follow-up of 60 months (interquartile range: 48.6-64.4), 49 patients developed a PSH, 20 (27.8%) in the mesh group and 29 (37.2%) in the nonmesh group (P = 0.22; RD: -9.4%; 95% CI: -24, 5.5). The cost related to the meshing strategy was € 2.239 lower than the nonmesh strategy (95% CI: 491.18, 3985.49), and quality-adjusted life years did not differ significantly between groups (P = 0.959; 95% CI: -0.066, 0.070).
Conclusions: Prophylactic mesh placement during the formation of an end-colostomy is a safe procedure but does not reduce the incidence of PSH after 5 years of follow-up. It does, however, delay the onset of PSH without a significant difference in morbidity, mortality, or quality of life, and seems to be cost-effective.

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Impact factor: 10.1; Q1

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5. Radiofrequency localization of nonpalpable breast cancer in a multicentre prospective cohort study: feasibility, clinical acceptability, and safety
Christenhusz A, den Dekker BM, van Dalen T, Jongen L, van der Schaaf MC, Alic L, Ten Haken B, Pijnappel RM, Dassen AE.

Purpose: In breast conserving surgery, accurate lesion localization is essential for obtaining adequate surgical margins. Preoperative wire localization (WL) and radioactive seed localization (RSL) are widely accepted methods to guide surgical excision of nonpalpable breast lesions but are limited by logistical challenges, migration issues, and legislative complexities. Radiofrequency identification (RFID) technology may offer a viable alternative. The purpose of this study was to evaluate the feasibility, clinical acceptability, and safety of RFID surgical guidance for localization of nonpalpable breast cancer.
Methods: In a prospective multicentre cohort study, the first 100 RFID localization procedures were included. The primary outcome was the percentage of clear resection margins and re-excision rate.

Secondary outcomes included procedure details, user experience, learningcurve, and adverse events.
Results: Between April 2019 and May 2021, 100 women underwent RFID guided breast conserving surgery. Clear resection margins were obtained in 89 out of 96 included patients (92.7%), re-excision was indicated in three patients (3.1%). Radiologists reported difficulties with the placement of the RFID tag, partially related to the relatively large needle-applicator (12-gauge). This led to the premature termination of the study in the hospital using RSL as regular care. The radiologist experience was improved after a manufacturer modification of the needle-applicator. Surgical localization involved a low learning curve. Adverse events (n = 33) included dislocation of the marker during insertion (8%) and hematomas (9%). The majority of adverse events (85%) occurred using the first-generation needle-applicator.
Conclusion: RFID technology is a potential alternative for non-radioactive and non-wire localization of nonpalpable breast lesions.

Gepubliceerd: Breast Cancer Res Treat. 2023;201(1):67-75.
Impact factor: 3.8 ; Q2

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6. Surgical Outcome After Pancreatoduodenectomy for Duodenal Adenocarcinoma Compared with Other Periampullary Cancers: A Nationwide Audit Study
de Bakker JK, Suurmeijer JA, Toennaer JGJ, Bonsing BA, Busch OR, van Eijck CH, de Hingh IH, de Meijer VE, Molenaar IQ, van Santvoort HC, Stommel MW, Festen S, van der Harst E, Patijn G, Lips DJ, Den Dulk M, Bosscha K, Besselink MG, Kazemier G.

Background: Surgical outcome after pancreatoduodenectomy for duodenal adenocarcinoma could differ from pancreatoduodenectomy for other cancers, but large multicenter series are lacking. This study aimed to determine surgical outcome in patients after pancreatoduodenectomy for duodenal adenocarcinoma, compared with other periampullary cancers, in a nationwide multicenter cohort.
Methods: After pancreatoduodenectomy for cancer between 2014 and 2019, consecutive patients were included from the nationwide, mandatory Dutch Pancreatic Cancer Audit. Patients were stratified by diagnosis. Baseline, treatment characteristics, and postoperative outcome were compared between groups. The association between diagnosis and major complications (Clavien-Dindo grade III or higher) was assessed via multivariable regression analysis.
Results: Overall, 3113 patients, after pancreatoduodenectomy for cancer, were included in this study: 264 (8.5%) patients with duodenal adenocarcinomas and 2849 (91.5%) with other cancers. After pancreatoduodenectomy for duodenal adenocarcinoma, patients had higher rates of major complications (42.8% vs. 28.6%; $p < 0.001$), postoperative pancreatic fistula (International Study Group of Pancreatic Surgery [ISGPS] grade B/C; 23.1% vs. 13.4%; $p < 0.001$), complication-related intensive care admission (14.3% vs. 10.3%; $p = 0.046$), re-interventions (39.8% vs. 26.6%; $p < 0.001$), in-hospital mortality (5.7% vs. 3.1%; $p = 0.025$), and longer hospital stay (15 days vs. 11 days; $p < 0.001$) compared with pancreatoduodenectomy for other cancers. In multivariable analysis, duodenal adenocarcinoma was independently associated with major complications (odds ratio 1.14, 95% confidence interval 1.03-1.27; $p = 0.011$).
Conclusion: Pancreatoduodenectomy for duodenal adenocarcinoma is associated with higher rates of major complications, pancreatic fistula, re-interventions, and in-hospital mortality compared with patients undergoing pancreatoduodenectomy for other cancers. These findings should be considered in patient counseling and postoperative management.

Gepubliceerd: Ann Surg Oncol. 2023;30(4):2448-55.
Impact factor: 3.7 ; Q1

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7. Minimally invasive versus open pancreatoduodenectomy for pancreatic and peri-ampullary neoplasm (DIPLOMA-2): study protocol for an international multicenter patient-blinded randomized controlled trial
de Graaf N, Emmen A, Ramera M, Björnsson B, Boggi U, Bruna CL, Busch OR, Daams F, Ferrari G, Festen S, van Hilst J, D'Hondt M, Ielpo B, Keck T, Khatkov IE, Koerkamp BG, Lips DJ, Luyer MDP, Mieog JSD, Morelli L, Molenaar IQ, van Santvoort HC, Sprangers MAG, Ferrari C, Berkhof J, Maisonneuve P, Abu Hilal M, Besselink MG.

Background: Minimally invasive pancreatoduodenectomy (MIPD) aims to reduce the negative impact of surgery as compared to open pancreatoduodenectomy (OPD) and is increasingly becoming part of clinical practice for selected patients worldwide. However, the safety of MIPD remains a topic of debate and the potential shorter time to functional recovery needs to be confirmed. To guide safe implementation of MIPD, large-scale international randomized trials comparing MIPD and OPD in experienced high-volume centers are needed. We hypothesize that MIPD is non-inferior in terms of overall complications, but superior regarding time to functional recovery, as compared to OPD.
Methods/design: The DIPLOMA-2 trial is an international randomized controlled, patient-blinded, non-inferiority trial performed in 14 high-volume pancreatic centers in Europe with a minimum annual volume of 30 MIPD and 30 OPD. A total of 288 patients with an indication for elective pancreatoduodenectomy for pre-malignant and malignant disease, eligible for both open and minimally invasive approach, are randomly allocated for MIPD or OPD in a 2:1 ratio. Centers perform either laparoscopic or robot-assisted MIPD based on their surgical expertise. The primary outcome is the Comprehensive Complication Index (CCI®), measuring all complications graded according to the Clavien-Dindo classification up to 90 days after surgery. The sample size is calculated with the following assumptions: 2.5% one-sided significance level (α), 80% power (1-β), expected difference of the mean CCI® score of 0 points between MIPD and OPD, and a non-inferiority margin of 7.5 points. The main secondary outcome is time to functional recovery, which will be analyzed for superiority. Other secondary outcomes include post-operative 90-day Fitbit™ measured activity, operative outcomes (e.g., blood loss, operative time, conversion to open surgery, surgeon-reported outcomes), oncological findings in case of malignancy (e.g., R0-resection rate, time to adjuvant treatment, survival), postoperative outcomes (e.g., clinically relevant complications), healthcare resource utilization (length of stay, readmissions, intensive care stay), quality of life, and costs. Postoperative follow-up is up to 36 months.
Discussion: The DIPLOMA-2 trial aims to establish the safety of MIPD as the new standard of care for this selected patient population undergoing pancreatoduodenectomy in high-volume centers, ultimately aiming for superior patient recovery.
Trial registration: ISRCTN27483786. Registered on August 2, 2023.

Gepubliceerd: Trials. 2023;24(1):665.
Impact factor: 2.5 ; Q3

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8. Survival of patients with colorectal liver metastases treated with and without preoperative chemotherapy: Nationwide propensity score-matched study
de Graaff MR, Klaase JM, van Dam RM, Kuhlmann KFD, Kazemier G, Swijnenburg RJ, Elfrink AKE, Verhoef C, Mieog JS, van den Boezem PB, Gobardhan P, Rijken AM, Lips DJ, Leclercq WGK, Marsman HA, van Duijvendijk P, van der Hoeven JAB, Vermaas M, Dulk MD, Grünhagen DJ, Kok NFM.

Introduction: Routine treatment with preoperative systemic chemotherapy (CTx) in patients with colorectal liver metastases (CRLM) remains controversial due to lack of consistent evidence demonstrating associated survival benefits. This study aimed to determine the effect of preoperative CTx on overall survival (OS) compared to surgery alone and to assess hospital and oncological network variation in 5-year OS.

Methods: This was a population-based study of all patients who underwent liver resection for CRLM between 2014 and 2017 in the Netherlands. After 1:1 propensity score matching (PSM), OS was compared between patients treated with and without preoperative CTx. Hospital and oncological network variation in 5-year OS corrected for case-mix factors was calculated using an observed/expected ratio.
Results: Of 2820 patients included, 852 (30.2%) and 1968 (69.8%) patients were treated with preoperative CTx and surgery alone, respectively. After PSM, 537 patients remained in each group, median number of CRLM; 3 [IQR 2-4], median size of CRLM; 28 mm [IQR 18-44], synchronous CLRM (71.1%). Median follow-up was 80.8 months. Five-year OS rates after PSM for patients treated with and without preoperative chemotherapy were 40.2% versus 38.3% (log-rank P = 0.734). After stratification for low, medium, and high tumour burden based on the tumour burden score (TBS) OS was similar for preoperative chemotherapy vs. surgery alone (log-rank P = 0.486, P = 0.914, and P = 0.744, respectively). After correction for non-modifiable patient and tumour characteristics, no relevant hospital or oncological network variation in five-year OS was observed.
Conclusion: In patients eligible for surgical resection, preoperative chemotherapy does not provide an overall survival benefit compared to surgery alone.

Gepubliceerd: Eur J Surg Oncol. 2023;49(9):106932.
Impact factor: 3.8 ; Q1

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9. 2 days versus 5 days of postoperative antibiotics for complex appendicitis: a pragmatic, open-label, multicentre, non-inferiority randomised trial
de Wijkerslooth EML, Boerma EG, van Rossem CC, van Rosmalen J, Baeten CIM, Beverdam FH, Bosmans J, Consten ECJ, Dekker JWT, Emous M, van Geloven AAW, Gijsen AF, Heijnen LA, Jairam AP, Melles DC, van der Ploeg APT, Steenvoorde P, Toorenvliet BR, Vermaas M, Wiering B, Wijnhoven BPL, van den Boom AL.

Background: The appropriate duration of postoperative antibiotics for complex appendicitis is unclear. The increasing global threat of antimicrobial resistance warrants restrictive antibiotic use, which could also reduce side-effects, length of hospital stay, and costs.
Methods: In this pragmatic, open-label, non-inferiority trial in 15 hospitals in the Netherlands, patients with complex appendicitis (aged ≥8 years) were randomly assigned (1:1) to receive 2 days or 5 days of intravenous antibiotics after appendicectomy. Randomisation was stratified by centre, and treating physicians and patients were not masked to treatment allocation. The primary endpoint was a composite endpoint of infectious complications and mortality within 90 days. The main outcome was the absolute risk difference (95% CI) in the primary endpoint, adjusted for age and severity of appendicitis, with a non-inferiority margin of 7·5%. Outcome assessment was based on electronic patient records and a telephone consultation 90 days after appendicectomy. Efficacy was analysed in the intention-to-treat and per-protocol populations. Safety outcomes were analysed in the intention-to-treat population. This trial was registered with the Netherlands Trial Register, NL5946.
Findings: Between April 12, 2017, and June 3, 2021, 13 267 patients were screened and 1066 were randomly assigned, 533 to each group. 31 were excluded from intention-to-treat analysis of the 2-day group and 30 from the 5-day group owing to errors in recruitment or consent. Appendicectomy was done laparoscopically in 955 (95%) of 1005 patients. The telephone follow-up was completed in 664 (66%) of 1005 patients. The primary endpoint occurred in 51 (10%) of 502 patients analysed in the 2-day group and 41 (8%) of 503 patients analysed in the 5-day group (adjusted absolute risk difference 2·0%, 95% CI -1·6 to 5·6). Rates of complications and re-interventions were similar between trial groups. Fewer patients had adverse effects of antibiotics in the 2-day group (45 [9%] of 502 patients) than in the 5-day group (112 [22%] of 503 patients; odds ratio [OR] 0·344, 95% CI 0·237 to 0·498). Re-admission to hospital was more frequent in the 2-day group (58 [12%] of 502 patients) than in the 5-day group (29 [6%] of 503 patients; OR 2·135, 1·342 to 3·396). There were no treatment-related

deaths.
Interpretation: 2 days of postoperative intravenous antibiotics for complex appendicitis is non-inferior to 5 days in terms of infectious complications and mortality within 90 days, based on a non-inferiority margin of 7·5%. These findings apply to laparoscopic appendicectomy conducted in a well resourced health-care setting. Adopting this strategy will reduce adverse effects of antibiotics and length of hospital stay.
Funding: The Netherlands Organization for Health Research and Development.

Gepubliceerd: Lancet. 2023;401(10374):366-76.
Impact factor: 168.9 ; Q1

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10. Factors associated with successful median arcuate ligament release in an international, multi-institutional cohort
DeCarlo C, Woo K, van Petersen AS, Geelkerken RH, Chen AJ, Yeh SL, Kim GY, Henke PK, Tracci MC, Schneck MB, Grotemeyer D, Meyer B, DeMartino RR, Wilkins PB, Iranmanesh S, Rastogi V, Aulivola B, Korepta LM, Shutze WP, Jett KG, Sorber R, Abularrage CJ, Long GW, Bove PG, Davies MG, Miserlis D, Shih M, Yi J, Gupta R, Loa J, Robinson DA, Gombert A, Doukas P, de Caridi G, Benedetto F, Wittgen CM, Smeds MR, Sumpio BE, Harris S, Szeberin Z, Pomozi E, Stilo F, Montelione N, Mouawad NJ, Lawrence P, Dua A.

Objective: Prior research on median arcuate ligament syndrome has been limited to institutional case series, making the optimal approach to median arcuate ligament release (MALR) and resulting outcomes unclear. In the present study, we compared the outcomes of different approaches to MALR and determined the predictors of long-term treatment failure.
Methods: The Vascular Low Frequency Disease Consortium is an international, multi-institutional research consortium. Data on open, laparoscopic, and robotic MALR performed from 2000 to 2020 were gathered. The primary outcome was treatment failure, defined as no improvement in median arcuate ligament syndrome symptoms after MALR or symptom recurrence between MALR and the last clinical follow-up.
Results: For 516 patients treated at 24 institutions, open, laparoscopic, and robotic MALR had been performed in 227 (44.0%), 235 (45.5%), and 54 (10.5%) patients, respectively. Perioperative complications (ileus, cardiac, and wound complications; readmissions; unplanned procedures) occurred in 19.2% (open, 30.0%; laparoscopic, 8.9%; robotic, 18.5%; P < .001). The median follow-up was 1.59 years (interquartile range, 0.38-4.35 years). For the 488 patients with follow-up data available, 287 (58.8%) had had full relief, 119 (24.4%) had had partial relief, and 82 (16.8%) had derived no benefit from MALR. The 1- and 3-year freedom from treatment failure for the overall cohort was 63.8% (95% confidence interval [CI], 59.0%-68.3%) and 51.9% (95% CI, 46.1%-57.3%), respectively. The factors associated with an increased hazard of treatment failure on multivariable analysis included robotic MALR (hazard ratio [HR], 1.73; 95% CI, 1.16-2.59; P = .007), a history of gastroparesis (HR, 1.83; 95% CI, 1.09-3.09; P = .023), abdominal cancer (HR, 10.3; 95% CI, 3.06-34.6; P < .001), dysphagia and/or odynophagia (HR, 2.44; 95% CI, 1.27-4.69; P = .008), no relief from a celiac plexus block (HR, 2.18; 95% CI, 1.00-4.72; P = .049), and an increasing number of preoperative pain locations (HR, 1.12 per location; 95% CI, 1.00-1.25; P = .042). The factors associated with a lower hazard included increasing age (HR, 0.99 per increasing year; 95% CI, 0.98-1.0; P = .012) and an increasing number of preoperative diagnostic gastrointestinal studies (HR, 0.84 per study; 95% CI, 0.74-0.96; P = .012) Open and laparoscopic MALR resulted in similar long-term freedom from treatment failure. No radiographic parameters were associated with differences in treatment failure.
Conclusions: No difference was found in long-term failure after open vs laparoscopic MALR; however, open release was associated with higher perioperative morbidity. These results support the use of a preoperative celiac plexus block to aid in patient selection. Operative candidates for MALR should be

counseled regarding the factors associated with treatment failure and the relatively high overall rate of treatment failure.

Gepubliceerd: J Vasc Surg. 2023;77(2):567-77.e2.
Impact factor: 4.3 ; Q1

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11. Predictive value of baseline serum carbohydrate antigen 19-9 level on treatment effect of neoadjuvant chemoradiotherapy in patients with resectable and borderline resectable pancreatic cancer in two randomized trials
Doppenberg D, van Dam JL, Han Y, Bonsing BA, Busch OR, Festen S, van der Harst E, de Hingh IH, Homs MYV, Kwon W, Lee M, Lips DJ, de Meijer VE, Molenaar IQ, Nuyttens JJ, Patijn GA, van Roessel S, van der Schelling GP, Suker M, Versteijne E, de Vos-Geelen J, Wilmink JW, van Eijck CHJ, van Tienhoven G, Jang JY, Besselink MG, Groot Koerkamp B.

Background: Guidelines suggest that the serum carbohydrate antigen (CA19-9) level should be used when deciding on neoadjuvant treatment in patients with resectable and borderline resectable pancreatic ductal adenocarcinoma (hereafter referred to as pancreatic cancer). In patients with resectable pancreatic cancer, neoadjuvant therapy is advised when the CA19-9 level is 'markedly elevated'. This study investigated the impact of baseline CA19-9 concentration on the treatment effect of neoadjuvant chemoradiotherapy (CRT) in patients with resectable and borderline resectable pancreatic cancers.
Methods: In this post hoc analysis, data were obtained from two RCTs that compared neoadjuvant CRT with upfront surgery in patients with resectable and borderline resectable pancreatic cancers. The effect of neoadjuvant treatment on overall survival was compared between patients with a serum CA19-9 level above or below 500 units/ml using the interaction test.
Results: Of 296 patients, 179 were eligible for analysis, 90 in the neoadjuvant CRT group and 89 in the upfront surgery group. Neoadjuvant CRT was associated with superior overall survival (HR 0.67, 95 per cent c.i. 0.48 to 0.94; P = 0.019). Among 127 patients (70, 9 per cent) with a low CA19-9 level, median overall survival was 23.5 months with neoadjuvant CRT and 16.3 months with upfront surgery (HR 0.63, 0.42 to 0.93). For 52 patients (29 per cent) with a high CA19-9 level, median overall survival was 15.5 months with neoadjuvant CRT and 12.9 months with upfront surgery (HR 0.82, 0.45 to 1.49). The interaction test for CA19-9 level exceeding 500 units/ml on the treatment effect of neoadjuvant CRT was not significant (P = 0.501).
Conclusion: Baseline serum CA19-9 level defined as either high or low has prognostic value, but was not associated with the treatment effect of neoadjuvant CRT in patients with resectable and borderline resectable pancreatic cancers, in contrast with current guideline advice.

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Impact factor: 9.6 ; Q1

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12. Diagnostic potential of plasma biomarkers and exhaled volatile organic compounds in predicting the different stages of acute mesenteric ischaemia: protocol for a multicentre prospective observational study (TACTIC study)
Duivenvoorden AAM, Clarysse M, Ceulemans LJ, Geelkerken RH, Derikx JPM, de Vries JPM, Buscher H, Olde Damink SWM, van Schooten FJ, Lubbers T, Lenaerts K.

Introduction: Acute mesenteric ischaemia (AMI) is a life-threatening condition with short-term mortality of up to 80%. The diagnosis of AMI has remained troublesome due to the non-specific clinical presentation, symptoms and laboratory findings. Early unambiguous diagnosis of AMI is

critical to prevent progression from reversible to irreversible transmural intestinal damage, thereby decreasing morbidity and improving survival. The present study aims to validate a panel of plasma biomarkers and investigate volatile organic compound (VOC) profiles in exhaled air as a tool to timely and accurately diagnose AMI.
Methods and analysis: In this international multicentre prospective observational study, 120 patients (>18 years of age) will be recruited with clinical suspicion of AMI. Clinical suspicion is based on: (1) clinical manifestation, (2) physical examination, (3) laboratory measurements and (4) the physician's consideration to perform a CT scan. The patient's characteristics, repetitive blood samples and exhaled air will be prospectively collected. Plasma levels of mucosal damage markers intestinal fatty acid-binding protein and villin-1, as well as transmural damage marker smooth muscle protein 22-alpha, will be assessed by ELISA. Analysis of VOCs in exhaled air will be performed by gas chromatography time-of-flight mass spectrometry. Diagnosis of AMI will be based on CT, endovascular and surgical reports, clinical findings, and (if applicable) verified by histopathological examination.
Ethics and dissemination: The study protocol was approved by the Medical Research Ethics Committee (METC) of Maastricht University Medical Centre+ and Maastricht University (METC azM/UM), the Netherlands (METC19-010) and the Ethics Committee Research UZ/KU Leuven, Belgium (S63500). Executive boards and local METCs of other Dutch participating centres Gelre Ziekenhuizen (Apeldoorn), Medisch Spectrum Twente (Enschede), and University Medical Centre Groningen have granted permission to carry out this study. Study results will be disseminated via open-access peer-reviewed scientific journals and national/international conferences.
Trial registration number: NCT05194527.

Gepubliceerd: BMJ Open. 2023;13(8):e072875.
Impact factor: 2.9 ; Q2

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13. Robot-assisted and fluorescence-guided remnant-cholecystectomy: a prospective dual-center cohort study
Gijsen AF, Vaassen HGM, Vahrmeijer AL, Geelkerken RH, Liem MSL, Bockhorn M, El-Sourani N, Mieog JSD, Lips DJ.

Background: Abdominal symptoms after cholecystectomy may be caused by gallstones in a remnant gallbladder or a long cystic duct stump. Resection of a remnant gallbladder or cystic duct stump is associated with an increased risk of conversion and bile duct or vascular injuries. We prospectively investigated the additional value of robotic assistance and fluorescent bile duct illumination in redo biliary surgery.
Methods: In this prospective two-centre observational cohort study, 28 patients were included with an indication for redo biliary surgery because of remnant stones in a remnant gallbladder or long cystic duct stump. Surgery was performed with the da Vinci X® and Xi® robotic system. The biliary tract was visualised in the fluorescence Firefly® mode shortly after intravenous injection of indocyanine green.
Results: There were no conversions or perioperative complications, especially no vascular or bile duct injuries. Fluorescence-based illumination of the extrahepatic bile ducts was successful in all cases. Symptoms were resolved in 27 of 28 patients. Ten patients were treated in day care and 13 patients were discharged the day after surgery.
Conclusion: Robot-assisted fluorescence-guided surgery for remnant gallbladder or cystic duct stump resection is safe, effective and can be done in day-care setting.

Gepubliceerd: HPB (Oxford). 2023;25(7):820-5.
Impact factor: 2.9 ; Q2

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

Görgec 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.

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.
Background: 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 9 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 analysis for blood loss.
Results: Of 9437 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 (interquartile range 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 (interquartile range 2-5) and 30-day/in-hospital mortality 0.8% (n=3). The R0 resection rate was 83.2% (n=263). Cumulative sum 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 seem favorable, future prospective studies should determine its added value.

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Impact factor: 10.1; Q1

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15. Practice variation in venous resection during pancreatoduodenectomy for pancreatic cancer: A nationwide cohort study

Groen JV, Michiels N, Besselink MG, Bosscha K, Busch OR, van Dam R, van Eijck CHJ, Koerkamp BG, van der Harst E, de Hingh IH, Karsten TM, Lips DJ, de Meijer VE, Molenaar IQ, Nieuwenhuijs VB, Roos D, van Santvoort HC, Wijsman JH, Wit F, Zonderhuis BM, de Vos-Geelen J, Wasser MN, Bonsing BA, Stommel MWJ, Mieog JSD.

Background: Practice variation exists in venous resection during pancreatoduodenectomy, but little is known about the potential causes and consequences as large studies are lacking. This study explores the potential causes and consequences of practice variation in venous resection during pancreatoduodenectomy for pancreatic cancer in the Netherlands.
Methods: This nationwide retrospective cohort study included patients undergoing pancreatoduodenectomy for pancreatic cancer in 18 centers from 2013 through 2017.
Results: Among 1,311 patients undergoing pancreatoduodenectomy, 351 (27%) had a venous resection, and the overall median annual center volume of venous resection was 4. No association

was found between the center volume of pancreatoduodenectomy and the rate of venous resections, nor between patient and tumor characteristics and the rate of venous resections per center. Female sex, lower body mass index, neoadjuvant therapy, venous involvement, and stenosis on imaging were predictive for venous resection. Adjusted for these factors, 3 centers performed significantly more, and 3 centers performed significantly fewer venous resections than expected. In patients with venous resection, significantly less major morbidity (22% vs 38%) and longer overall survival (median 16 vs 12 months) were observed in centers with an above-median annual volume of venous resections (>4). **Conclusion**: Patient and tumor characteristics did not explain significant practice variation between centers in the Netherlands in venous resection during pancreatoduodenectomy for pancreatic cancer. The clinical outcomes of venous resection might be related to the volume of the procedure.

Gepubliceerd: Surgery. 2023;174(4):924-33.
Impact factor: 3.8 ; Q1

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16. Endoscopic ultrasonography-guided gastroenterostomy versus surgical gastrojejunostomy for palliation of malignant gastric outlet obstruction (ENDURO): study protocol for a randomized controlled trial

Kastelijn JB, van de Pavert YL, Besselink MG, Fockens P, Voermans RP, van Wanrooij RLJ, de Wijkerslooth TR, Curvers WL, de Hingh I, Bruno MJ, Koerkamp BG, Patijn GA, Poen AC, van Hooft JE, Inderson A, Mieog JSD, Poley JW, Bijlsma A, Lips DJ, Venneman NG, Verdonk RC, van Dullemen HM, Hoogwater FJH, Frederix GWJ, Molenaar IQ, Welsing PMJ, Moons LMG, van Santvoort HC, Vleggaar FP.

Background: Malignant gastric outlet obstruction (GOO) is a debilitating condition that frequently occurs in patients with malignancies of the distal stomach and (peri)ampullary region. The standard palliative treatment for patients with a reasonable life expectancy and adequate performance status is a laparoscopic surgical gastrojejunostomy (SGJ). Recently, endoscopic ultrasound-guided gastroenterostomy (EUS-GE) emerged as a promising alternative to the surgical approach. The present study aims to compare these treatment modalities in terms of efficacy, safety, and costs.
Methods: The ENDURO-study is a multicentre, open-label, parallel-group randomized controlled trial. In total, ninety-six patients with gastric outlet obstruction caused by an irresectable or metastasized malignancy will be 1:1 randomized to either SGJ or EUS-GE. The primary endpoint is time to tolerate at least soft solids. The co-primary endpoint is the proportion of patients with persisting or recurring symptoms of gastric outlet obstruction for which a reintervention is required. Secondary endpoints are technical and clinical success, quality of life, gastroenterostomy dysfunction, reinterventions, time to reintervention, adverse events, quality of life, time to start chemotherapy, length of hospital stay, readmissions, weight, survival, and costs.
Discussion: The ENDURO-study assesses whether EUS-GE, as compared to SGJ, results in a faster resumption of solid oral intake and is non-inferior regarding reinterventions for persistent or recurrent obstructive symptoms in patients with malignant GOO. This trial aims to guide future treatment strategies and to improve quality of life in a palliative setting.
Trial registration: International Clinical Trials Registry Platform (ICTRP): NL9592. Registered on 07 July 2021.

Gepubliceerd: Trials. 2023;24(1):608.
Impact factor: 2.5 ; Q3

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17. Minimally invasive versus open distal pancreatectomy for resectable pancreatic cancer (DIPLOMA): an international randomised non-inferiority trial

Korrel M, Jones LR, van Hilst J, Balzano G, Björnsson B, Boggi U, Bratlie SO, Busch OR, Butturini G, Capretti G, Casadei R, Edwin B, Emmen A, Esposito A, Falconi M, Groot Koerkamp B, Keck T, de Kleine RHJ, Kleive DB, Kokkola A, Lips DJ, Lof S, Luyer MDP, Manzoni A, Marudanayagam R, de Pastena M, Pecorelli N, Primrose JN, Ricci C, Salvia R, Sandström P, Vissers F, Wellner UF, Zerbi A, Dijkgraaf MGW, Besselink MG, Abu Hilal M.

Background: The oncological safety of minimally invasive surgery has been questioned for several abdominal cancers. Concerns also exist regarding the use of minimally invasive distal pancreatectomy (MIDP) in patients with resectable pancreatic cancer as randomised trials are lacking.
Methods: In this international randomised non-inferiority trial, we recruited adults with resectable pancreatic cancer from 35 centres in 12 countries. Patients were randomly assigned to either MIDP (laparoscopic or robotic) or open distal pancreatectomy (ODP). Both patients and pathologists were blinded to the assigned approach. Primary endpoint was radical resection (R0, ≥1 mm free margin) in patients who had ultimately undergone resection. Analyses for the primary endpoint were by modified intention-to-treat, excluding patients with missing data on primary endpoint. The pre-defined non-inferiority margin of -7% was compared with the lower limit of the two-sided 90% confidence interval (CI) of absolute difference in the primary endpoint. This trial is registered with the ISRCTN registry (ISRCTN44897265).
Findings: Between May 8, 2018 and May 7, 2021, 258 patients were randomly assigned to MIDP (131 patients) or ODP (127 patients). Modified intention-to-treat analysis included 114 patients in the MIDP group and 110 patients in the ODP group. An R0 resection occurred in 83 (73%) patients in the MIDP group and in 76 (69%) patients in the ODP group (difference 3.7%, 90% CI -6.2 to 13.6%; p(non-inferiority) = 0.039). Median lymph node yield was comparable (22.0 [16.0-30.0] vs 23.0 [14.0-32.0] nodes, p = 0.86), as was the rate of intraperitoneal recurrence (41% vs 38%, p = 0.45). Median follow-up was 23.5 (interquartile range 17.0-30.0) months. Other postoperative outcomes were comparable, including median time to functional recovery (5 [95% CI 4.5-5.5] vs 5 [95% CI 4.7-5.3] days; p = 0.22) and overall survival (HR 0.99, 95% CI 0.67-1.46, p = 0.94). Serious adverse events were reported in 23 (18%) of 131 patients in the MIDP group vs 28 (22%) of 127 patients in the ODP group.
Interpretation: This trial provides evidence on the non-inferiority of MIDP compared to ODP regarding radical resection rates in patients with resectable pancreatic cancer. The present findings support the applicability of minimally invasive surgery in patients with resectable left-sided pancreatic cancer. FUNDING: Medtronic Covidien AG, Johnson & Johnson Medical Limited, Dutch Gastroenterology Society.

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Impact factor: 20.9 ; Q onbekend

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18. Both-Column Acetabular Fractures: Does Surgical Approach Vary Based on Using Virtual 3D Reconstructions?
Leemhuis JF, Assink N, Reininga IHF, de Vries JPM, Ten Duis K, Meesters AML, FFA IJpma, Pelvic Fracture Consortium Investigators: van Stigt SFL.

Displacement of the anterior and posterior column complicates decision making for both-column acetabular fractures. We questioned whether pelvic surgeons agree on treatment strategy, and whether the use of virtual 3D reconstructions changes the treatment strategy of choice. A nationwide cross-sectional survey was performed in all pelvic trauma centers in the Netherlands. Twenty surgeons assessed 15 both-column fractures in 2D as well as 3D. Based on conventional imaging, surgical treatment was recommended in 89% of cases, and by adding 3D reconstructions this was 93% (p = 0.09). Surgical approach was recommended as anterior (65%), posterior (8%) or combined (27%) (poor level of agreement, κ = 0.05) based on conventional imaging. The approach changed in 37% (p = 0.006), with most changes between a combined and anterior approach (still poor level of

agreement, κ = 0.13) by adding 3D reconstructions. Additionally, surgeons' level of confidence increased from good in 38% to good in 50% of cases. In conclusion, surgeons do not agree on the treatment strategy for both-column acetabular fractures. Additional information given by 3D reconstructions may change the chosen surgical approach and increase surgeons' confidence about their treatment decision. Therefore, virtual 3D reconstructions are helpful for assessing both-column fracture patterns and aid in the choice of treatment strategy.

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Impact factor: 3.6 ; Q2

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19. Ultrasound Particle Image Velocimetry to Investigate Potential Hemodynamic Causes of Limb Thrombosis After Endovascular Aneurysm Repair With the Anaconda Device
Mirgolbabaee H, van de Velde L, Geelkerken RH, Versluis M, Groot Jebbink E, Reijnen M.

Purpose: To identify potential hemodynamic predictors for limb thrombosis (LT) following endovascular aneurysm repair with the Anaconda endograft in a patient-specific phantom.
Materials and methods: A thin-walled flow phantom, based on a patient's aortic anatomy and treated with an Anaconda endograft, that presented with a left-sided LT was fabricated. Contrast-enhanced ultrasound particle image velocimetry was performed to quantify time-resolved velocity fields. Measurements were performed in the same phantom with and without the Anaconda endograft, to investigate the impact of the endograft on the local flow fields. Hemodynamic parameters, namely vector complexity (VC) and residence time (RT), were calculated for both iliac arteries.
Results: In both limbs, the vector fields were mostly unidirectional during the peak systolic and end-systolic velocity phases before and after endograft placement. Local vortical structures and complex flow fields were observed at the diastolic and transitional flow phases. The average VC was higher (0.11) in the phantom with endograft, compared to the phantom without endograft (0.05). Notably, in both left and right iliac arteries, the anterior wall regions corresponded to a 2- and 4-fold increase in VC in the phantom with endograft, respectively. RT simulations showed values of 1.3 to 6 seconds in the phantom without endograft. A higher RT (up to 25 seconds) was observed in the phantom with endograft, in which the left iliac artery, with LT in follow-up, showed 2 fluid stasis regions.
Conclusion: This in vitro study shows that unfavorable hemodynamics were present mostly in the limb that thrombosed during follow-up, with the highest VC and longest RT. These parameters might be valuable in predicting the occurrence of LT in the future.
Clinical impact: This in-vitro study aimed to identify potential hemodynamic predictors for limb thrombosis following EVAR using ultrasound particle image velocimetry (echoPIV) technique. It was shown that unfavorable hemodynamic norms were present mostly in the thrombosed limb. Owing to the in-vivo feasibility of the echoPIV, future efforts should focus on the evaluation of these hemodynamic norms in clinical trials. Thereafter, using echoPIV as a bedside technique in hospitals becomes more promising. Performing echoPIV in pre-op phase may provide valuable insights for surgeons to enhance treatment planning. EchoPIV is also applicable for follow-up sessions to evaluate treatment progress and avoid/predict complications.

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Impact factor: 2.6 ; Q2

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20. A Systematic Review of Endovascular Repair Outcomes in Atherosclerotic Chronic Mesenteric Ischaemia
Nana P, Koelemay MJW, Leone N, Brodis A, van den Berg JC, de Bruin JL, Geelkerken RH, Spanos K.

Objective: Chronic mesenteric ischaemia (CMI) treatment focuses on symptom relief and prevention of disease progression. Endovascular repair represents the main treatment modality, while data on the associated antiplatelet regimen are scarce. The aim of this meta-analysis was to assess the early and midterm outcomes of endovascular repair in patients with CMI.
Data sources: Randomised controlled trials and observational studies (1990 - 2022) reporting on early and midterm endovascular repair outcomes in patients with atherosclerotic CMI.
Review methods: The PRISMA guidelines and PICO model were followed. The protocol was registered to PROSPERO (CRD42023401685). Medline, Embase (via Ovid), and Cochrane databases were searched (end date 21 February 2023). The Newcastle-Ottawa Scale was used for risk of bias assessment, and GRADE for evidence quality assessment. Primary outcomes were technical success, 30 day mortality, and symptom relief, assessed using prevalence meta-analysis. The role of dual antiplatelet therapy (DAPT) was investigated using meta-regression analysis.
Results: Sixteen retrospective studies (1 224 patients; mean age 69.8 ± 10.6 years; 60.3% female) reporting on 1 368 target vessels (57.8% superior mesenteric arteries) were included. Technical success was 95.0% (95% CI 93 - 97%, p = .28, I(2) 19%, low certainty), the 30 day mortality rate was 2.0% (95% CI 2 - 4%, p = .93, I(2) 36%, low certainty), and immediate symptom relief was 87.0% (95% CI 80 - 92%, p < .010, I(2) 85%, very low certainty). At mean follow up of 28 months, the mortality rate was 15.0% (95% CI 9 - 25%, p = .010, I(2) 86%, very low certainty), symptom recurrence 25.0% (95% CI 21 - 31%, p < .010, I(2) 68%, very low certainty) and re-intervention rate 26.0% (95% CI 17 - 37%, p < .010, I(2) 92%, very low certainty). Single antiplatelet therapy (SAPT) and DAPT performed similarly in the investigated outcomes.
Conclusion: Endovascular repair for CMI appears to be safe as first line treatment, with a low peri-operative mortality rate and acceptable immediate symptom relief. During midterm follow up, symptom recurrence and need for re-intervention are not uncommon. SAPT appears to be equal to DAPT in post-operative outcomes.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2023;66(5):632-43.
If 5.7 ; Q1

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21. The PD-ROBOSCORE: A difficulty score for robotic pancreatoduodenectomy
Napoli N, Cacace C, Kauffmann EF, Jones L, Ginesini M, Gianfaldoni C, Salamone A, Asta F, Ripolli A, Di Dato A, Busch OR, Cappelle ML, Chao YJ, de Wilde RF, Hackert T, Jang JY, Koerkamp BG, Kwon W, Lips D, Luyer MDP, Nickel F, Saint-Marc O, Shan YS, Shen B, Vistoli F, Besselink MG, Hilal MA, Boggi U.

Background: Difficulty scoring systems are important for the safe, stepwise implementation of new procedures. We designed a retrospective observational study for building a difficulty score for robotic pancreatoduodenectomy.
Methods: The difficulty score (PD-ROBOSCORE) aims at predicting severe postoperative complications after robotic pancreatoduodenectomy. The PD-ROBOSCORE was developed in a training cohort of 198 robotic pancreatoduodenectomies and was validated in an international multicenter cohort of 686 robotic pancreatoduodenectomies. Finally, all centers tested the model during the early learning curve (n = 300). Growing difficulty levels (low, intermediate, high) were defined using cut-off values set at the 33rd and 66th percentile (NCT04662346).
Results: Factors included in the final multivariate model were a body mass index of ≥25 kg/m^2 for males and ≥30 kg/m^2 for females (odds ratio:2.39; P < .0001), borderline resectable tumor (odd ratio:1.98; P < .0001), uncinate process tumor (odds ratio:1.69; P < .0001), pancreatic duct size <4 mm (odds ratio:1.59; P < .0001), American Society of Anesthesiologists class ≥3 (odds ratio:1.59; P < .0001), and hepatic artery originating from the superior mesenteric artery (odds ratio:1.43; P < .0001). In the training cohort, the absolute score value (odds ratio = 1.13; P = .0089) and difficulty groups (odds ratio = 2.35; P = .041) predicted severe postoperative complications. In the multicenter

validation cohort, the absolute score value predicted severe postoperative complications (odds ratio = 1.16, P < .001), whereas the difficulty groups did not (odds ratio = 1.94, P = .082). In the learning curve cohort, both absolute score value (odds ratio:1.078, P = .04) and difficulty groups (odds ratio: 2.25, P = .017) predicted severe postoperative complications. Across all cohorts, a PD-ROBOSCORE of ≥12.51 doubled the risk of severe postoperative complications. The PD-ROBOSCORE score also predicted operative time, estimated blood loss, and vein resection. The PD-ROBOSCORE predicted postoperative pancreatic fistula, delayed gastric emptying, postpancreatectomy hemorrhage, and postoperative mortality in the learning curve cohort.
Conclusion: The PD-ROBOSCORE predicts severe postoperative complications after robotic pancreatoduodenectomy. The score is readily available via www.pancreascalculator.com.

Gepubliceerd: Surgery. 2023;173(6):1438-46.
Impact factor: 3.8 ; Q1

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22. Risk of bleeding after percutaneous coronary intervention and its impact on further adverse events in clinical trial participants with comorbid peripheral arterial disease
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: Both patients with obstructive coronary artery disease (CAD) and patients with peripheral arterial disease (PADs) have an increased bleeding risk. Information is scarce on bleeding in CAD patients, treated with percutaneous coronary intervention (PCI), who have comorbid PADs. We assessed whether PCI patients with PADs have a higher bleeding risk than PCI patients without PADs. Furthermore, in PCI patients with PADs we evaluated the extent by which bleeding increased the risk of further adverse events.
Methods: Three-year pooled patient-level data of two randomized PCI trials (BIO-RESORT, BIONYX) with drug-eluting stents were analyzed to assess mortality and the composite endpoint major adverse cardiac events (MACE: all-cause mortality, any myocardial infarction, emergent coronary artery bypass surgery, or target lesion revascularization).
Results: Among 5989 all-comer patients, followed for 3 years, bleeding occurred in 7.7% (34/440) with comorbid PADs and 5.0% (279/5549) without PADs (HR: 1.59, 95%CI: 1.11-2.23, p = 0.010). Of all PADs patients, those with a bleeding had significantly higher rates of all-cause mortality (HR: 4.70, 95%CI: 2.37-9.33, p < 0.001) and MACE (HR: 2.39, 95%CI: 1.23-4.31, p = 0.003). Furthermore, PADs patients with a bleeding were older (74.4 ± 6.9 vs. 67.4 ± 9.5, p < 0.001). After correction for age and other potential confounders, bleeding remained independently associated with all-cause mortality (adj.HR: 2.97, 95%CI: 1.37-6.43, p = 0.006) while the relation of bleeding with MACE became borderline non-significant (adj.HR: 1.85, 95%CI: 0.97-3.55, p = 0.06).
Conclusion: PCI patients with PADs had a higher bleeding risk than PCI patients without PADs. In PADs patients, bleeding was associated with all-cause mortality, even after adjustment for potential confounders.

Gepubliceerd: Int J Cardiol. 2023;374:27-32.
Impact factor: 3.5 ; Q2

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23. Outcome of percutaneous coronary intervention using ultrathin-strut biodegradable polymer sirolimus-eluting versus thin-strut durable polymer zotarolimus-eluting stents in patients with comorbid peripheral arterial disease: a post-hoc analysis from two randomized trials
Pinxterhuis TH, Ploumen EH, Zocca P, Doggen CJM, Schotborgh CE, Anthonio RL, Roguin A, Danse PW, Benit E, Aminian A, van Houwelingen KG, Linssen GCM, Geelkerken RH, von Birgelen C.

Background: In patients with peripheral arterial disease (PADs), who underwent percutaneous coronary intervention (PCI), little is known about the potential impact of using different new-generation drug-eluting stents (DES) on outcome. In PCI all-comers, the results of most between-stent comparisons-stratified by strut thickness-suggested some advantage of coronary stents with ultrathin-struts. The current post-hoc analysis aimed to assess outcomes of PCI with ultrathin-strut biodegradable polymer sirolimus-eluting stents (BP-SES) *vs.* thin-strut durable polymer zotarolimus-eluting stents (DP-ZES) in patients with PADs.
Methods: We pooled 3-year patient-level data from two large-scale randomized all-comer trials to compare Orsiro ultrathin-strut BP-SES *vs.* Resolute-type thin-strut DP-ZES in trial participants with concomitant PADs. BIO-RESORT (December 2012 to August 2015) and BIONYX (October 2015 to December 2016) included all-comer patients who were aged 18 years or older, capable of providing informed consent, and required a PCI. The trials had web-based randomization, with block sizes of 4 and 8, performed in a 1:1:1 or 1:1 fashion. Assessors, research staff, and patients were blinded to the type of stent used. We assessed the composite main clinical endpoint target vessel failure [TVF: cardiac death, target vessel related myocardial infarction (MI), or clinically indicated target vessel revascularization (TVR)], its components, and stent thrombosis.
Results: Of 4,830 trial participants, 360 had PADs: 177 (49.2%) were treated with BP-SES and 183 (50.8%) with DP-ZES. Baseline characteristics were similar. For BP-SES, the 3-year TVF rate was 11.0% and for DP-ZES 17.9% [hazard ratio (HR): 0.59, 95% CI: 0.33-1.04; P=0.07]. For BP-SES, the TVR rate was lower than for DP-ZES (4.1% *vs.* 11.0%; HR: 0.36, 95% CI: 0.15-0.86; P=0.016), but this did not translate into between-group differences in cardiac death or MI. In small vessels (<2.75 mm), the TVR rate was also lower in BP-SES (5.6% *vs.* 13.9%; HR: 0.32, 95% CI: 0.11-0.91; P=0.024). Definite-or-probable stent thrombosis rates were 1.2% and 2.3% (P=0.43).
Conclusions: In PCI patients with PADs, the 3-year TVF incidence was numerically lower in the ultrathin-strut BP-SES *vs.* the thin-strut DP-ZES group. Furthermore, TVR risk was significantly lower in ultrathin-strut BP-SES, mainly driven by a lower TVR rate in small vessels.
Trial registration: BIO-RESORT trial: *clinicaltrials.gov* (*NCT01674803*); BIONYX trial: *clinicaltrials.gov* (*NCT02508714*).

Gepubliceerd: Cardiovasc Diagn Ther. 2023;13(4):673-85.
Impact factor: 2.4 ; Q3

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24. Performance of the BioIntegral Bovine Pericardial Graft in Vascular Infections: VASCular No-REact Graft Against INfection Study
Reinders Folmer EI, Verhofstad N, Zeebregts CJ, van Sambeek M, Saleem BR, VASC-REGAIN collaborators: Willigendael EM.

Background: Vascular graft and endograft infections (VGEI) and native vessel infections (NVI) remain considerable challenges in vascular surgery, leading to high mortality and morbidity rates. Although in situ reconstruction is the preferred treatment, the material of choice is still a source of debate. Autologous veins are considered the first choice; however, xenografts may be an acceptable alternative. The performance of a biomodified bovine pericardial graft is assessed when implemented in an infected vascular area.
Methods: This is a prospective multicenter cohort study. Patients who underwent reconstruction for VGEI or NVI with a biomodified bovine pericardial bifurcated or straight tube graft were included from December 2017 until June 2021. The primary outcome measure was reinfection at mid-term follow-up. Secondary outcome measures included mortality, patency, and amputation rate.
Results: Thirty-four patients with vascular infections were included, of which 23 (68%) had an infected Dacron prosthesis after primary open repair and 8 (24%) had an infected endovascular graft. The remaining 3 (9%) had infected native vessels. At secondary repair, 3 (7%) patients had an in situ

aortic tube reconstruction, 29 (66%) had an aortic bifurcated reconstruction, and 2 (5%) had an iliac-femoral reconstruction. At 1-year follow-up after the BioIntegral bovine pericardial graft reconstruction, the reinfection rate was 9%. The 1-year infection-related and procedure-related mortality rate was 16%. The occlusion rate was 6% and in total 3 patients underwent a lower limb amputation during the 1-year follow-up period.
Conclusions: In situ reconstruction as treatment of (endo)graft and native vessel infections remains a challenge and reinfection looms as a potential consequence. In cases where time is of essence or when autologous venous repair is not feasible, a swift available solution is needed. The BioIntegral biomodified bovine pericardial graft may be an option as it shows reasonable results in terms of reinfection, in aortic tube and bifurcated grafts.

Gepubliceerd: Ann Vasc Surg. 2023;95:116-24.
Impact factor: 1.5 ; Q3

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25. Perprocedural Heparinization in Non-cardiac Arterial Procedures: The Current Practice in the Netherlands
Roosendaal LC, Hoebink M, Wiersema AM, Yeung KK, Blankensteijn JD, Jongkind V, ACTION-survey collaborators: Menting TP.

Purpose: Heparin is the most widely-used anticoagulant to prevent thrombo-embolic complications during non-cardiac arterial procedures (NCAP). Unfortunately, there is a lack of evidence and consequently non-uniformity in guidelines on perprocedural heparin management. Detailed insight into the current practice of antithrombotic strategies during NCAP in the Netherlands is important, aiming to identify potential optimal protocols and local differences concerning perprocedural heparinization.
Materials and methods: A comprehensive online survey was distributed electronically to vascular surgeons of every hospital in the Netherlands in which NCAP were performed. Data were collected from September 2020 to October 2021.
Results: The response rate was 90% (53/59 hospitals). During NCAP, all surgeons generally administered heparin before arterial clamping. In 74% (39/54) of hospitals, a single heparin dosing protocol was used for all types of patients and vascular procedures. In 40%, there was no uniformity in heparin dosing between vascular surgeons. Depending on the procedure, a fixed bolus heparin, predominantly 5000 IU, was administered in 73% to 93%. In the remaining hospitals (7%-27%), a bodyweight-based heparin protocol was used, with an initial dose of 70 or 100 IU/kg. A minority (28%) monitored the effect of heparin in patients using the activated clotting time add (ACT) after activated clotting time. Target values varied between 180 and 250 seconds or 2 times the baseline ACT.
Conclusion: This survey demonstrates considerable variability in perprocedural heparinization during NCAP in the Netherlands. Future research on heparin dosing is needed to harmonize and optimize heparin dosage protocols and contemporary guidelines during NCAP, and thereby improve vascular surgical care and patient safety.
Clinical impact: This survey demonstrated persisting intra- and inter-hospital variability in perprocedural heparinization during non-cardiac arterial procedures (NCAP) in the Netherlands. The observed variability in heparinization strategies highlights the need for high quality evidence on perprocedural anticoagulation strategies. This is needed in order to harmonize and optimize heparin dosage protocols and contemporary guidelines and thereby improve vascular surgical patient care. Based on the current results, an international survey will be conducted by the authors to gain additional insight into the antithrombotic strategies used during NCAP, aiming to harmonize anticoagulation protocols worldwide.

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Impact factor: 2.6 ; Q2

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26. Geometrical Changes of the Aorta as Predictors for Thromboembolic Events After EVAR With the Anaconda Stent-Graft
Simmering JA, de Vries M, Haalboom M, Reijnen M, Slump CH, Geelkerken RH.

Purpose: Thromboembolic events (TE), including limb graft occlusion (LGO) and distal limb embolization (DLE), are common complications after endovascular aneurysm repair (EVAR). The aim of this study was to find predictors for TE in patients treated with the Anaconda stent-graft for infrarenal aneurysms.
Materials and methods: Geometrical and anatomical variables were retrospectively analyzed in a consecutive Anaconda cohort. Pre- and postoperative CT scans were used to derive geometrical parameters length, curvature, torsion, and tortuosity index (TI) from the center lumen lines (CLLs). Limb characteristics, pre-to-post EVAR and mid-term-follow-up changes in the parameters were evaluated for their predictive value for TE.
Results: Eighty-four patients (mean age 74±8.3 years, 74 men) were enrolled. The risk of TE was lowered with pre-to-post implant decreasing TI (steps of 0.05: OR: 1.30, 95% CI: 1.01-1.66, p=0.04), pre-to-post implant decreasing mean curvature (OR: 1.08, 95% CI: 1.01-1.16, p=0.03), and a larger degree of circumferential common iliac artery (CIA) calcification (OR: 0.98, 95% CI: 0.97-1.00, p=0.03). The only LGO predictor was the caudal relocation of maximal curvature after EVAR (OR: 1.01, 95% CI: 1.00-1.01, p=0.04). Preventors of DLE were CIA diameter (OR: 0.87, 95% CI: 0.76-0.99, p=0.04), circumferential CIA calcification (OR: 0.97, 95% CI: 0.95-1.00, p=0.03), mean and maximal curvature of the preoperative aortoiliac trajectory (OR: 0.86, 95% CI: 0.79-0.94, p<0.01 and OR: 0.97, 95% CI: 0.95-1.00, p=0.03, respectively) and pre-to-postoperative decrease in mean curvature (OR: 1.11, 95% CI: 1.02-1.21, p=0.02). Midterm TE predictors were length (OR: 0.95, 95% CI: 0.89-1.01, p=0.08) and torsion maximum location (OR: 1.01, 95% CI: 0.99-1.01, p=0.10).
Conclusion: The present study confirms that treatment of infrarenal AAA with an Anaconda stent-graft is related to a relatively high TE rate which decreases with a pre-to-postoperative reduction in curvature and TI, and a larger degree of circumferential CIA calcification. In other words, more aortoiliac straightening and more circumferential CIA calcification may prevent TE development after EVAR with this stent-graft.

Gepubliceerd: J Endovasc Ther. 2023;30(6):904-19.
Impact factor: 2.6 ; Q2

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27. Renal and Visceral Artery Configuration During the First Year of Follow-Up After Fenestrated Aortic Aneurysm Repair Using the Anaconda Stent-graft: A Prospective Longitudinal Multicenter Study With ECG-Gated CTA Scans
Simmering JA, Koenrades MA, Slump CH, Groot Jebbink E, Zeebregts CJ, Reijnen M, Geelkerken RH.

Objective: The performance of fenestrated endovascular aortic aneurysm repair (FEVAR) may be compromised by complications related to the dynamic vascular environment. The aim of this study was to analyze the behavior of FEVAR bridging stent configurations during the cardiac cycle and during follow-up to improve our understanding on treatment durability.
Design: Twenty-one patients presenting with complex abdominal aortic aneurysms (AAAs; 9 juxtarenal/6 pararenal/3 paravisceral/1 thoracoabdominal aortic aneurysm type IV), treated with a fenestrated Anaconda (Terumo Aortic, Inchinnan, Scotland, UK) with Advanta V12 bridging stents (Getinge, Merrimack, NH, USA), were prospectively enrolled in a multicenter observational cohort

study and underwent electrocardiogram (ECG)-gated computed tomographic angiography (CTA) preoperatively, at discharge, 7-week, and 12-month follow-ups.
Methods: Fenestrated endovascular aortic aneurysm repair stability was assessed considering the following variables: branch angle as the angle between the aorta and the target artery, end-stent angle as the angle between the end of the bridging stent and the native artery downstream from it, curvature and tortuosity index (TI) to describe the bending of the target artery. Body-bridging stent stability was assessed considering bridging stent flare lengths, the distances between the proximal sealing stent-ring and fenestrations and the distance between the fenestration and first apposition in the target artery.
Results: Renal branch angles significantly increased after FEVAR toward a perpendicular position (right renal artery from median 60.9°, inter quartile range [IQR]=44.2-84.9° preoperatively to 94.4°, IQR=72.6-99.8°, p=0.001 at 12-month follow-up; left renal artery [LRA], from 63.7°, IQR=55.0-73.0° to 94.3°, IQR=68.2-105.6°, p<0.001), while visceral branch angles did not. The mean dynamic curvature only decreased for the LRA from preoperative (3.0, IQR=2.2-3.8 m^{-1}) to 12-month follow-up (1.9, IQR=1.4-2.6 m^{-1}, p=0.027). The remaining investigated variables did not seem to show any changes over time in this cohort.
Conclusions: Fenestrated endovascular aortic aneurysm repair for complex AAAs using the Anaconda fenestrated stent-graft and balloon-expandable Advanta V12 bridging stents demonstrated stable configurations up to 12-month follow-up, except for increasing renal branch angles toward perpendicular orientation to the aorta, yet without apparent clinical consequences in this cohort.
Clinical impact: This study provides detailed information on the cardiac-pulsatility-induced (dynamic) and longitudinal geometry deformations of the target arteries and bridging stents after fenestrated endovascular aortic aneurysm repair (FEVAR) up to 12-month follow-up. The configuration demonstrated limited dynamic and longitudinal deformations in terms of branch angle, end-stent angle, curvature, and tortuosity index (TI), except for the increasing renal branch angles that go toward a perpendicular orientation to the aorta. Overall, the results suggest that the investigated FEVAR configurations are stable and durable, though careful consideration of increasing renal branch angles and significant geometry alterations is advised.

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Impact factor: 2.6 ; Q2

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28. In Vivo Quantification of Cardiac-Pulsatility-Induced Motion Before and After Double-Branched Endovascular Aortic Arch Repair
Simmering JA, Leeuwerke SJG, Meerwaldt R, Zeebregts CJ, Slump CH, Geelkerken RH.

The Relay(®)Branch stent-graft (Terumo Aortic, Sunrise, FL, USA) offers a custom-made endovascular solution for complex aortic arch pathologies. In this technical note, a modified electrocardiography (ECG)-gated computed tomography (CT)-based algorithm was applied to quantify cardiac-pulsatility-induced changes of the aortic arch geometry and motion before and after double-branched endovascular repair (bTEVAR) of an aortic arch aneurysm. This software algorithm has the potential to provide novel and clinically relevant insights in the influence of bTEVAR on aortic anatomy, arterial compliance, and stent-graft dynamics.

Gepubliceerd: J Endovasc Ther. 2023;30(4):510-9.
Impact factor: 2.6 ; Q2

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29. Differences in Cardiac-Pulsatility-Induced Displacement and Geometry Changes between the Cook ZBIS and Gore IBE: Postoperative Comparison Using ECG-Gated CTA Scans

Simmering JA, van Helvert M, van Herwaarden JA, Slump CH, Geelkerken RH, Reijnen M.

To what extent the stentgraft design of iliac branch devices (IBDs) relates to dynamic deformation is currently unknown. Therefore, this study aimed to quantify and compare displacement and geometry changes during the cardiac cycle of two common IBDs. This paper presents a two-center trial with patients treated with a Zenith bifurcated iliac side (ZBIS) or Gore iliac branch endoprosthesis (IBE). All patients underwent a retrospective electrocardiogram (ECG)-gated computed tomographic angiography (CTA) during follow-up. Cardiac-pulsatility-induced displacement was quantified for the following locations: (neo) bifurcation of the aorta, IBD flow divider, distal markers of the internal iliac artery (IIA) component and first IIA bifurcation. Geometrical parameters (length, tortuosity index, curvature and torsion) were quantified over centerlines. Displacement was more pronounced for the IBE than the ZBIS, e.g., craniocaudal displacement of 0.91 mm (0.91-1.13 mm) vs. 0.57 mm (0.40-0.75 mm, p = 0.004), respectively. The IBDs demonstrated similar geometrical parameters in the neo-common iliac artery and distal IIA, except for the larger dynamic curvature and torsion of the distal IIA in IBEs. The IBEs showed more dynamic length and curvature change compared to the ZBIS in the stented IIA. The IIA trajectory showed more pronounced deformation during the cardiac cycle after placement of an IBE than a ZBIS, suggesting the IBE is more conformable than the ZBIS.

Gepubliceerd: Diagnostics (Basel). 2023;13(3).
Impact factor: 3.6 ; Q2

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30. The influence of electrocardiogram-gated computed tomography reconstruction into 8 or 10 cardiac phases on cardiac-pulsatility-induced motion quantification of stent grafts in the aorta
Simmering JA, Zagers DA, Geelkerken RH, Kuipers H, Te Riet OGSGA, Reijnen M, Slump CH.

Objective: The goal of this study was to determine to what extent aortic stent graft motion quantification is comparable between electrocardiogram (ECG)-gated computed tomography (CT) scans with reconstructions into 8 and 10 cardiac phases on CT scanners from two different vendors.
Methods: An experimental setup that induces motion of an aortic stent graft, according to a predefined aortic blood pressure wave, was placed in two CT scanners of different vendors. The stent graft motion was captured using an ECG-gated CT technique and quantified using dedicated analysis algorithms. The calculated motion amplitudes and total traveled path lengths of stent segmentations were compared between scans reconstructed into 8 and 10 phases and between the scanners, after validation with sensor measurements and repeated measurements.
Results: No difference in motion amplitudes in z-direction (craniocaudal direction) was observed between the reconstructions into 8 and 10 phases (0.02 mm; 95% confidence interval [CI], -0.01 to 0.05 mm; *P* = .358). The z-amplitudes differed by 0.04 mm (95% CI, 0.01-0.07 mm; *P* = .003) between the different CT scanners. Path lengths differed 0.07 mm (95% CI, 0.01-to 0.13 mm; *P* = .013) between the reconstructions into 8 and 10 phases and 0.13 mm (95% CI, 0.06-0.17 mm; *P* < .001) between the different scanners.
Conclusions: The motion amplitudes can accurately be compared between 8 and 10 phases and between the two scanners, without differences larger than the voxel size of 0.3 × 0.3 × 0.5 mm. Clinical motion analysis results of different ECG-gated CT scans and CT scanners can be compared up to the accuracy of the CT scan.

Gepubliceerd: JVS Vasc Sci. 2023;4:100131.
Impact factor: onbekend

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31. Evaluation of National Surgical Practice for Lateral Lymph Nodes in Rectal Cancer in an Untrained Setting

Sluckin TC, Hazen SJA, Horsthuis K, Beets-Tan RGH, Aalbers AGJ, Beets GL, Boerma EG, Borstlap J, van Breest Smallenburg V, Burger JWA, Crolla R, Daniëls-Gooszen AW, Davids PHP, Dunker MS, Fabry HFJ, Furnée EJB, van Gils RAH, de Haas RJ, Hoogendoorn S, van Koeverden S, de Korte FI, Oosterling SJ, Peeters K, Posma LAE, Pultrum BB, Rothbarth J, Rutten HJT, Schasfoort RA, Schreurs WH, Simons PCG, Smits AB, Talsma AK, The GYM, van Tilborg F, Tuynman JB, Vanhooymissen IJS, van de Ven AWH, Verdaasdonk EGG, Vermaas M, Vliegen RFA, Vogelaar FJ, de Vries M, Vroemen JC, van Vugt ST, Westerterp M, van Westreenen HL, de Wilt JHW, van der Zaag ES, Zimmerman DDE, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group: van Duyn EB.

Background: Involved lateral lymph nodes (LLNs) have been associated with increased local recurrence (LR) and ipsi-lateral LR (LLR) rates. However, consensus regarding the indication and type of surgical treatment for suspicious LLNs is lacking. This study evaluated the surgical treatment of LLNs in an untrained setting at a national level.
Methods: Patients who underwent additional LLN surgery were selected from a national cross-sectional cohort study regarding patients undergoing rectal cancer surgery in 69 Dutch hospitals in 2016. LLN surgery consisted of either 'node-picking' (the removal of an individual LLN) or 'partial regional node dissection' (PRND; an incomplete resection of the LLN area). For all patients with primarily enlarged (≥7 mm) LLNs, those undergoing rectal surgery with an additional LLN procedure were compared to those undergoing only rectal resection.
Results: Out of 3057 patients, 64 underwent additional LLN surgery, with 4-year LR and LLR rates of 26% and 15%, respectively. Forty-eight patients (75%) had enlarged LLNs, with corresponding recurrence rates of 26% and 19%, respectively. Node-picking (n = 40) resulted in a 20% 4-year LLR, and a 14% LLR after PRND (n = 8; p = 0.677). Multivariable analysis of 158 patients with enlarged LLNs undergoing additional LLN surgery (n = 48) or rectal resection alone (n = 110) showed no significant association of LLN surgery with 4-year LR or LLR, but suggested higher recurrence risks after LLN surgery (LR: hazard ratio [HR] 1.5, 95% confidence interval [CI] 0.7-3.2, p = 0.264; LLR: HR 1.9, 95% CI 0.2-2.5, p = 0.874).
Conclusion: Evaluation of Dutch practice in 2016 revealed that approximately one-third of patients with primarily enlarged LLNs underwent surgical treatment, mostly consisting of node-picking. Recurrence rates were not significantly affected by LLN surgery, but did suggest worse outcomes. Outcomes of LLN surgery after adequate training requires further research.

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Impact factor: 3.7 ; Q1

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32. The Areola study: design and rationale of a cohort study on long-term health outcomes in women with implant-based breast reconstructions

Spoor J, Mureau MAM, Hommes J, Rakhorst H, Dassen AE, Oldenburg HSA, Vissers YLJ, Heuts EM, Koppert LB, Zaal LH, van der Hulst R, Vrancken Peeters M, Bleiker EMA, van Leeuwen FE.

Background: Implant-based breast reconstructions contribute considerably to the quality of life of breast cancer patients. A knowledge gap exists concerning the potential role of silicone breast implants in the development of so-called "breast implant illness" (BII) and autoimmune diseases in breast cancer survivors with implant-based reconstructions. BII is a constellation of non-specific symptoms reported by a small group of women with silicone breast implants.
Methods: The Areola study is a multicenter retrospective cohort study with prospective follow-up aiming to assess the risk of BII and autoimmune diseases in female breast cancer survivors with and without silicone breast implants. In this report, we set out the rationale, study design, and methodology of this cohort study. The cohort consists of breast cancer survivors who received

surgical treatment with implant-based reconstruction in six major hospitals across the Netherlands in the period between 2000 and 2015. As a comparison group, a frequency-matched sample of breast cancer survivors without breast implants will be selected. An additional group of women who received breast augmentation surgery in the same years will be selected to compare their characteristics and health outcomes with those of breast cancer patients with implants. All women who are still alive will be invited to complete a web-based questionnaire covering health-related topics. The entire cohort including deceased women will be linked to population-based databases of Statistics Netherlands. These include a registry of hospital diagnostic codes, a medicines prescription registry, and a cause-of-death registry, through which diagnoses of autoimmune diseases will be identified. Outcomes of interest are the prevalence and incidence of BII and autoimmune diseases. In addition, risk factors for the development of BII and autoimmune disorders will be assessed among women with implants.
Discussion: The Areola study will contribute to the availability of reliable information on the risks of BII and autoimmune diseases in Dutch breast cancer survivors with silicone breast implants. This will inform breast cancer survivors and aid future breast cancer patients and their treating physicians to make informed decisions about reconstructive strategies after mastectomy.
Registration: This study is registered at ClinicalTrials.gov on June 2, 2022 (NCT05400954).

Gepubliceerd: Ann Epidemiol. 2023;82:16-25.
Impact factor: 5.6 ; Q1

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33. Pancreatectomy with arterial resection for periampullary cancer: outcomes after planned or unplanned events in a nationwide, multicentre cohort
Stoop TF, Mackay TM, Brada LJH, van der Harst E, Daams F, Land FRV, Kazemier G, Patijn GA, van Santvoort HC, de Hingh IH, Bosscha K, Seelen LWF, Nijkamp MW, Stommel MWJ, Liem MSL, Busch OR, Coene PLO, van Dam RM, de Wilde RF, Mieog JSD, Quintus Molenaar I, Besselink MG, van Eijck CHJ.

Gepubliceerd: Br J Surg. 2023;110(6):638-42.
Impact factor: 9.6 ; Q1

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34. Outcome of Pancreatic Surgery During the First 6 Years of a Mandatory Audit Within the Dutch Pancreatic Cancer Group
Suurmeijer JA, Henry AC, Bonsing BA, Bosscha K, van Dam RM, van Eijck CH, Gerhards MF, van der Harst E, de Hingh IH, Intven MP, Kazemier G, Wilmink JW, Lips DJ, Wit F, de Meijer VE, Molenaar IQ, Patijn GA, van der Schelling GP, Stommel MWJ, Busch OR, Groot Koerkamp B, van Santvoort HC, Besselink MG.

Objective: To describe outcome after pancreatic surgery in the first 6 years of a mandatory nationwide audit.
Background: Within the Dutch Pancreatic Cancer Group, efforts have been made to improve outcome after pancreatic surgery. These include collaborative projects, clinical auditing, and implementation of an algorithm for early recognition and management of postoperative complications. However, nationwide changes in outcome over time have not yet been described.
Methods: This nationwide cohort study included consecutive patients after pancreatoduodenectomy (PD) and distal pancreatectomy from the mandatory Dutch Pancreatic Cancer Audit (January 2014-December 2019). Patient, tumor, and treatment characteristics were compared between 3 time periods (2014-2015, 2016-2017, and 2018-2019). Short-term surgical outcome was investigated using multilevel multivariable logistic regression analyses. Primary endpoints were failure to rescue (FTR) and in-hospital mortality.

Results: Overall, 5345 patients were included, of whom 4227 after PD and 1118 after distal pancreatectomy. After PD, FTR improved from 13% to 7.4% [odds ratio (OR) 0.64, 95% confidence interval (CI) 0.50-0.80, P <0.001] and in-hospital mortality decreased from 4.1% to 2.4% (OR 0.68, 95% CI 0.54-0.86, P =0.001), despite operating on more patients with age >75 years (18%-22%, P =0.006), American Society of Anesthesiologists score ≥3 (19%-31%, P <0.001) and Charlson comorbidity score ≥2 (24%-34%, P <0.001). The rates of textbook outcome (57%-55%, P =0.283) and major complications remained stable (31%-33%, P =0.207), whereas complication-related intensive care admission decreased (13%-9%, P =0.002). After distal pancreatectomy, improvements in FTR from 8.8% to 5.9% (OR 0.65, 95% CI 0.30-1.37, P =0.253) and in-hospital mortality from 1.6% to 1.3% (OR 0.88, 95% CI 0.45-1.72, P =0.711) were not statistically significant.
Conclusions: During the first 6 years of a nationwide audit, in-hospital mortality and FTR after PD improved despite operating on more high-risk patients. Several collaborative efforts may have contributed to these improvements.

Gepubliceerd: Ann Surg. 2023;278(2):260-6.
Impact factor: 10.1; Q1

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35. Nationwide Outcome after Pancreatoduodenectomy in Patients at very High Risk (ISGPS-D) for Postoperative Pancreatic Fistula
Theijse RT, Stoop TF, Hendriks TE, Suurmeijer JA, Smits FJ, Bonsing BA, Lips DJ, Manusama E, van der Harst E, Patijn GA, Wijsman JH, Meerdink M, den Dulk M, van Dam R, Stommel MWJ, van Laarhoven K, de Wilde RF, Festen S, Draaisma WA, Bosscha K, van Eijck CHJ, Busch OR, Molenaar IQ, Groot Koerkamp B, van Santvoort HC, Besselink MG.

Objective: To assess nationwide surgical outcome after pancreatoduodenectomy (PD) in patients at very high risk for postoperative pancreatic fistula (POPF), categorized as ISGPS-D.
Summary background data: Morbidity and mortality after ISGPS-D PD is perceived so high that a recent randomized trial advocated prophylactic total pancreatectomy (TP) as alternative aiming to lower this risk. However, current outcomes of ISGPS-D PD remain unknown as large nationwide series are lacking.
Methods: Nationwide retrospective analysis including consecutive patients undergoing ISGPS-D PD (i.e., soft texture and pancreatic duct ≤3 mm), using the mandatory Dutch Pancreatic Cancer Audit (2014-2021). Primary outcome was in-hospital mortality and secondary outcomes included major morbidity (i.e., Clavien-Dindo grade ≥IIIa) and POPF (ISGPS grade B/C). The use of prophylactic TP to avoid POPF during the study period was assessed.
Results: Overall, 1402 patients were included. In-hospital mortality was 4.1% (n=57), which decreased to 3.7% (n=20/536) in the last 2 years. Major morbidity occurred in 642 patients (45.9%) and POPF in 410 (30.0%), which corresponded with failure to rescue in 8.9% (n=57/642). Patients with POPF had increased rates of major morbidity (88.0% vs. 28.3%; P<0.001) and mortality (6.3% vs. 3.5%; P=0.016), compared to patients without POPF. Among 190 patients undergoing TP, prophylactic TP to prevent POPF was performed in 4 (2.1%).
Conclusion: This nationwide series found a 4.1% in-hospital mortality after ISGPS-D PD with 45.9% major morbidity, leaving little room for improvement through prophylactic TP. Nevertheless, given the outcomes in 30% of patients who develop POPF, future randomized trials should aim to prevent and mitigate POPF in this high-risk category.

Gepubliceerd: Ann Surg. 2023.
Impact factor: 10.1; Q1

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36. Persistent and new-onset symptoms after cholecystectomy in patients with uncomplicated symptomatic cholecystolithiasis: A post hoc analysis of 2 prospective clinical trials
Thunnissen FM, Baars C, Arts R, Latenstein CSS, Drenth JPH, van Laarhoven C, Lantinga MA, de Reuver PR, Dutch Gallbladder Research Group: Steenvoorde P.

Background: Laparoscopic cholecystectomy is the gold standard for treating biliary colic in patients with gallstones, but post-cholecystectomy abdominal pain is commonly reported. This study investigates which symptoms are likely to persist and which may develop after a cholecystectomy.
Methods: Patients from 2 previous prospective trials who underwent laparoscopic cholecystectomy for symptomatic cholecystolithiasis were included. Patients completed questionnaires on pain and gastrointestinal symptoms before surgery and at 6 months follow-up. The prevalence of persistent and new-onset abdominal symptoms was evaluated.
Results: A total of 820 patients received cholecystectomy and were included, 75.4% female (n = 616/820) mean age 49.4 years (standard deviation 13.7). At baseline, 74.1% (n = 608/820) of patients met all criteria for biliary colic. Cholecystectomy successfully resolved biliary colic in 94.8% (n = 327/345) of patients, but 36.5% (n = 299/820) of patients reported persistent abdominal pain after 6 months of follow-up. The prevalence of most abdominal symptoms reduced significantly. Symptoms such as flatulence (17.8%, n = 146/820) or restricted eating (14.5%, n = 119/820) persisted most often. New-onset symptoms were frequent bowel movements (9.6%, n = 79/820), bowel urgency (8.5%, n = 70/820), and new-onset diarrhea (8.4%, 69/820).
Conclusion: Postcholecystectomy symptoms are mainly flatulence, frequent bowel movements, and restricted eating. Newly reported symptoms are mainly frequent bowel movements, bowel urgency, and diarrhea. The present findings give clinical guidance in informing, managing, and treating patients with symptoms after cholecystectomy.

Gepubliceerd: Surgery. 2023;174(4):781-6.
Impact factor: 3.8 ; Q1

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37. Erratum to "Practice variation in anastomotic leak after esophagectomy: Unravelling differences in failure to rescue" [Eur J Surg Oncol 49 (5) (May 2023) 974-982]
Ubels S, Matthée E, Verstegen M, Klarenbeek B, Bouwense S, van Berge Henegouwen MI, Daams F, Dekker JWT, van Det MJ, van Esser S, Griffiths EA, Haveman JW, Nieuwenhuijzen G, Siersema PD, Wijnhoven B, Hannink G, van Workum F, Rosman C, TENTACLE – Esophagus collaborative group: Mastboom W, Steenvoorde P.

Gepubliceerd: Eur J Surg Oncol. 2023;49(9):106993.
Impact factor: 3.8 ; Q1

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38. Practice variation in anastomotic leak after esophagectomy: Unravelling differences in failure to rescue
Ubels S, Matthée E, Verstegen M, Klarenbeek B, Bouwense S, van Berge Henegouwen MI, Daams F, Dekker JWT, van Det MJ, van Esser S, Griffiths EA, Haveman JW, Nieuwenhuijzen G, Siersema PD, Wijnhoven B, Hannink G, van Workum F, Rosman C, Heisterkamp J, Polat F, Schouten J, Singh P, study collaborators: Mastboom W, Steenvoorde P.

Introduction: Failure to rescue (FTR) is an important outcome measure after esophagectomy and reflects mortality after postoperative complications. Differences in FTR have been associated with hospital resection volume. However, insight into how centers manage complications and achieve their outcomes is lacking. Anastomotic leak (AL) is a main contributor to FTR. This study aimed to

assess differences in FTR after AL between centers, and to identify factors that explain these differences.
Methods: TENTACLE - Esophagus is a multicenter, retrospective cohort study, which included 1509 patients with AL after esophagectomy. Differences in FTR were assessed between low-volume (<20 resections), middle-volume (20-60 resections) and high-volume centers (≥60 resections). Mediation analysis was performed using logistic regression, including possible mediators for FTR: case-mix, hospital resources, leak severity and treatment.
Results: FTR after AL was 11.7%. After adjustment for confounders, FTR was lower in high-volume vs. low-volume (OR 0.44, 95%CI 0.2-0.8), but not versus middle-volume centers (OR 0.67, 95%CI 0.5-1.0). After mediation analysis, differences in FTR were found to be explained by lower leak severity, lower secondary ICU readmission rate and higher availability of therapeutic modalities in high-volume centers. No statistically significant direct effect of hospital volume was found: high-volume vs. low-volume 0.86 (95%CI 0.4-1.7), high-volume vs. middle-volume OR 0.86 (95%CI 0.5-1.4).
Conclusion: Lower FTR in high-volume compared with low-volume centers was explained by lower leak severity, less secondary ICU readmissions and higher availability of therapeutic modalities. To reduce FTR after AL, future studies should investigate effective strategies to reduce leak severity and prevent secondary ICU readmission.

Gepubliceerd: Eur J Surg Oncol. 2023;49(5):974-82.
Impact factor: 3.8 ; Q1

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39. Treatment of anastomotic leak after oesophagectomy for oesophageal cancer: large, collaborative, observational TENTACLE cohort study
Ubels S, Verstegen MHP, Klarenbeek BR, Bouwense S, van Berge Henegouwen MI, Daams F, van Det MJ, Griffiths EA, Haveman JW, Heisterkamp J, Nieuwenhuijzen G, Polat F, Schouten J, Siersema PD, Singh P, Wijnhoven B, Hannink G, van Workum F, Rosman C, TENTACLE – Esophagus collaborative group: Mastboom W, Steenvoorde P.

Background: Anastomotic leak is a severe complication after oesophagectomy. Anastomotic leak has diverse clinical manifestations and the optimal treatment strategy is unknown. The aim of this study was to assess the efficacy of treatment strategies for different manifestations of anastomotic leak after oesophagectomy.
Methods: A retrospective cohort study was performed in 71 centres worldwide and included patients with anastomotic leak after oesophagectomy (2011-2019). Different primary treatment strategies were compared for three different anastomotic leak manifestations: interventional versus supportive-only treatment for local manifestations (that is no intrathoracic collections; well perfused conduit); drainage and defect closure versus drainage only for intrathoracic manifestations; and oesophageal diversion versus continuity-preserving treatment for conduit ischaemia/necrosis. The primary outcome was 90-day mortality. Propensity score matching was performed to adjust for confounders.
Results: Of 1508 patients with anastomotic leak, 28.2 per cent (425 patients) had local manifestations, 36.3 per cent (548 patients) had intrathoracic manifestations, 9.6 per cent (145 patients) had conduit ischaemia/necrosis, 17.5 per cent (264 patients) were allocated after multiple imputation, and 8.4 per cent (126 patients) were excluded. After propensity score matching, no statistically significant differences in 90-day mortality were found regarding interventional versus supportive-only treatment for local manifestations (risk difference 3.2 per cent, 95 per cent c.i. -1.8 to 8.2 per cent), drainage and defect closure versus drainage only for intrathoracic manifestations (risk difference 5.8 per cent, 95 per cent c.i. -1.2 to 12.8 per cent), and oesophageal diversion versus continuity-preserving treatment for conduit ischaemia/necrosis (risk difference 0.1 per cent, 95 per cent c.i. -21.4 to 1.6 per cent). In general, less morbidity was found after less extensive primary treatment strategies.

Conclusion: Less extensive primary treatment of anastomotic leak was associated with less morbidity. A less extensive primary treatment approach may potentially be considered for anastomotic leak. Future studies are needed to confirm current findings and guide optimal treatment of anastomotic leak after oesophagectomy.

Gepubliceerd: Br J Surg. 2023;110(7):852-63.
Impact factor: 9.6 ; Q1

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40. Twelve-year outcomes of watchful waiting versus surgery of mildly symptomatic or asymptomatic inguinal hernia in men aged 50 years and older: a randomised controlled trial
Van den Dop LM, Van Egmond S, Heijne J, van Rosmalen J, de Goede B, Wijsmuller AR, Kleinrensink GJ, Tanis PJ, Jeekel J, Lange JF, INCA Trialists' Collaboration: Mastboom W.

Background: Inguinal hernia belongs to the most common surgical pathology worldwide. Approximately, one third is asymptomatic. The value of watchful waiting (WW) in patients with asymptomatic or mildly symptomatic inguinal hernia has been established in a few randomised controlled trials (RCTs). The aim of this study was to assess long-term outcomes of a RCT comparing WW and elective surgery.
Methods: In the original study, men aged ≥50 years with an asymptomatic or mildly symptomatic inguinal hernia were randomly assigned to WW or elective repair. In the present study, the primary outcome was the 12-year crossover rate to surgery, secondary outcomes were time-to-crossover, patient regret, pain, quality of life and incarceration. Dutch Trial Registry: NTR629.
Findings: Out of 496 originally analysed patients, 488 (98.4%) were evaluable for chart review (WW: n = 258, surgery: n = 230), and 200 (41.0%) for telephone contact (WW: n = 106, surgery: n = 94) between November 2021 and March 2022 with a median 12 years follow-up (IQR 9-14). After 12 years, the estimated cumulative crossover rate to surgery was 64.2%, which was higher in mildly symptomatic than in asymptomatic patients (71.7% versus 60.4%, HR 1.451, 95% CI: 1.064-1.979). Time-to-crossover was longer in asymptomatic patients (50% after 6.0 years versus 2.0 years, p = 0.019). Patient regret was higher in the WW group (37.7 versus 18.0%, p = 0.002), as well as pain/discomfort (p = 0.031). Quality of life did not differ (p = 0.737). In the WW group, incarceration occurred in 10/255 patients (3.9%).
Interpretation: During 12-year follow-up, most WW patients crossed over to surgery, significantly earlier with mildly symptomatic hernia. Considering the relatively low incarceration rate, WW might still be an option in asymptomatic patients with a clear preference and being well-informed about pros and cons.
Funding: The initial trial was funded by the Netherlands Organisation for Health Research and Development (ZonMW). This long-term study did not receive funding.

Gepubliceerd: EClinicalMedicine. 2023;64:102207.
Impact factor: 15.1 ; Q1

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41. A personalized app to improve quality of life of patients with a stoma: A protocol for a multicentre randomized controlled trial
van der Storm SL, Bemelman WA, van Dieren S, Schijven MP, Stoma APPtimize Collaborative Study group: van Duyn EB.

Aim: Proper education, guidance and support is crucial before and following creation of a stoma. Patients with a stoma and their close relatives need to adapt to and cope with this new - and sometimes unforeseen - situation, which may result in insecurities and a variety of psychosocial

problems. Self-efficacy is associated both with a reduction in psychosocial problems and with improved quality of life. The main objective of this study was to investigate whether self-reported quality of life of patients with a stoma can be enhanced by offering personalized and timed guidance, as well as peer contact, in a patient-centred mobile application.
Method: A multicentre, double-blind, randomized controlled trial will be conducted. Consented adults >18 years of age who will receive an ileostomy or colostomy and possess an eligible smartphone will be included. The intervention group will be given the full version of the application (containing personalized and timed guidance, such as operation-specific information and information on the associated care pathway) to install on their smartphone. In addition, the intervention group has access to a protected peer-support platform within the app. The control group will receive a restricted version of the application that contains only generic (non-personalized) stoma-related information. The primary outcome is quality of life, 3 months postoperatively. Secondary outcomes are Patient Reported Outcome Measures (PROMs), such as psychological adaption, as well as number of complications, re-admission and re-operation rates and the length of hospital stay.
Results: Patient enrolment began in March 2021. Data collection was not complete when this protocol was submitted.
Conclusion: We hypothesize that patients with a stoma who are supported by the intervention version of the app will report a significantly higher quality of life than patients with a stoma who are supported by the control version of the app (ie, are not offered personalized and timed guidance and information and do not have access to peer support in the app).

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Impact factor: 3.4 ; Q1

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42. Endograft position and endoleak detection after endovascular abdominal aortic repair with low-field tiltable MRI: a feasibility study
van Zandwijk JK, Schuurmann RCL, Haken BT, Stassen CM, Geelkerken RH, de Vries JPM, Simonis FFJ.

Background: Abdominal aortic endoleaks after endovascular aneurysm repair might be position-dependent, therefore undetectable using supine imaging. We aimed to determine the feasibility and benefit of using a low-field tiltable magnetic resonance imaging (MRI) scanner allowing to study patients who can be imaged in both supine and upright positions of endoleaks.
Methods: Ten EVAR patients suspected of endoleak based on ultrasound examination were prospectively included. MRI in upright and supine positions was compared with routine supine computed tomography angiography (CTA). Analysis was performed through (1) subjective image quality assessment by three observers, (2) landmark registration between MRI and CTA scans, (3) Euclidean distances between renal and endograft landmarks, and (4) evaluation of endoleak detection on MRI by a consensus panel. Statistical analysis was performed by one-way repeated measures analysis of variance.
Results: The image quality of upright/supine MRI was inferior compared to CTA. Median differences in both renal and endograft landmarks were approximately 6-7 mm between upright and supine MRI and 5-6 mm between supine MRI and CTA. In the proximal sealing zone of the endograft, no differences were found among all three scan types ($p = 0.264$). Endoleak detection showed agreement between MRI and CTA in 50% of the cases, with potential added value in only one patient.
Conclusions: The benefit of low-field upright MRI for endoleak detection was limited. While MRI assessment was non-inferior to standard CTA in detecting endoleaks in selected cases, improved hardware and sequences are needed to explore the potential of upright MRI in patients with endoleaks.
Relevance statement: Upright low-field MRI has limited clinical value in detecting position-dependent endoleaks; improvements are required to fulfil its potential as a complementary modality in this clinical setting.

Key points: • Upright MRI shows potential for imaging endoleaks in aortic aneurysm patients in different positions. • The image quality of upright MRI is inferior to current techniques. • Upright MRI complements CTA, but lacks accurate deformation measurements for clinical use. • Advancements in hardware and imaging sequences are needed to fully utilise upright MRI capabilities.

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Impact factor: 3.8 ; Q onbekend

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43. The Feasibility, Proficiency, and Mastery Learning Curves in 635 Robotic Pancreatoduodenectomies Following a Multicenter Training Program: "Standing on the Shoulders of Giants"

Zwart MJW, van den Broek B, de Graaf N, Suurmeijer JA, Augustinus S, Te Riele WW, van Santvoort HC, Hagendoorn J, Borel Rinkes IHM, van Dam JL, Takagi K, Tran KTC, Schreinemakers J, van der Schelling G, Wijsman JH, de Wilde RF, Festen S, Daams F, Luyer MD, de Hingh I, Mieog JSD, Bonsing BA, Lips DJ, Abu Hilal M, Busch OR, Saint-Marc O, Zeh HJ, 3rd, Zureikat AH, Hogg ME, Koerkamp BG, Molenaar IQ, Besselink MG.

Objective: To assess the feasibility, proficiency, and mastery learning curves for robotic pancreatoduodenectomy (RPD) in "second-generation" RPD centers following a multicenter training program adhering to the IDEAL framework.
Background: The long learning curves for RPD reported from "pioneering" expert centers may discourage centers interested in starting an RPD program. However, the feasibility, proficiency, and mastery learning curves may be shorter in "second-generation" centers that participated in dedicated RPD training programs, although data are lacking. We report on the learning curves for RPD in "second-generation" centers trained in a dedicated nationwide program.
Methods: Post hoc analysis of all consecutive patients undergoing RPD in 7 centers that participated in the LAELAPS-3 training program, each with a minimum annual volume of 50 pancreatoduodenectomies, using the mandatory Dutch Pancreatic Cancer Audit (March 2016-December 2021). Cumulative sum analysis determined cutoffs for the 3 learning curves: operative time for the feasibility (1) risk-adjusted major complication (Clavien-Dindo grade ≥III) for the proficiency, (2) and textbook outcome for the mastery, (3) learning curve. Outcomes before and after the cutoffs were compared for the proficiency and mastery learning curves. A survey was used to assess changes in practice and the most valued "lessons learned."
Results: Overall, 635 RPD were performed by 17 trained surgeons, with a conversion rate of 6.6% (n=42). The median annual volume of RPD per center was 22.5±6.8. From 2016 to 2021, the nationwide annual use of RPD increased from 0% to 23% whereas the use of laparoscopic pancreatoduodenectomy decreased from 15% to 0%. The rate of major complications was 36.9% (n=234), surgical site infection 6.3% (n=40), postoperative pancreatic fistula (grade B/C) 26.9% (n=171), and 30-day/in-hospital mortality 3.5% (n=22). Cutoffs for the feasibility, proficiency, and mastery learning curves were reached at 15, 62, and 84 RPD. Major morbidity and 30-day/in-hospital mortality did not differ significantly before and after the cutoffs for the proficiency and mastery learning curves. Previous experience in laparoscopic pancreatoduodenectomy shortened the feasibility (-12 RPDs, -44%), proficiency (-32 RPDs, -34%), and mastery phase learning curve (-34 RPDs, -23%), but did not improve clinical outcome.
Conclusions: The feasibility, proficiency, and mastery learning curves for RPD at 15, 62, and 84 procedures in "second-generation" centers after a multicenter training program were considerably shorter than previously reported from "pioneering" expert centers. The learning curve cutoffs and prior laparoscopic experience did not impact major morbidity and mortality. These findings demonstrate the safety and value of a nationwide training program for RPD in centers with sufficient volume.

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Impact factor: 10.1; Q1

Totale impact factor: 397.8
Gemiddelde impact factor: 9.3

Aantal artikelen 1e, 2e of laatste auteur: 8
Totale impact factor: 23.8
Gemiddelde impact factor: 3.0

Intensive care

1. Association between prehospital end-tidal carbon dioxide levels and mortality in patients with suspected severe traumatic brain injury
Bossers SM, Mansvelder F, Loer SA, Boer C, Bloemers FW, Van Lieshout EMM, Den Hartog D, Hoogerwerf N, van der Naalt J, Absalom AR, Schwarte LA, Twisk JWR, Schober P, BRAIN-PROTECT Collaborators: Beishuizen A.

Purpose: Severe traumatic brain injury is a leading cause of mortality and morbidity, and these patients are frequently intubated in the prehospital setting. Cerebral perfusion and intracranial pressure are influenced by the arterial partial pressure of CO_2 and derangements might induce further brain damage. We investigated which lower and upper limits of prehospital end-tidal CO_2levels are associated with increased mortality in patients with severe traumatic brain injury.
Methods: The BRAIN-PROTECT study is an observational multicenter study. Patients with severe traumatic brain injury, treated by Dutch Helicopter Emergency Medical Services between February 2012 and December 2017, were included. Follow-up continued for 1 year after inclusion. End-tidal CO_2 levels were measured during prehospital care and their association with 30-day mortality was analyzed with multivariable logistic regression.
Results: A total of 1776 patients were eligible for analysis. An L-shaped association between end-tidal CO_2 levels and 30-day mortality was observed (p = 0.01), with a sharp increase in mortality with values below 35 mmHg. End-tidal CO_2 values between 35 and 45 mmHg were associated with better survival rates compared to < 35 mmHg. No association between hypercapnia and mortality was observed. The odds ratio for the association between hypocapnia (< 35 mmHg) and mortality was 1.89 (95% CI 1.53-2.34, p < 0.001) and for hypercapnia (≥ 45 mmHg) 0.83 (0.62-1.11, p = 0.212).
Conclusion: A safe zone of 35-45 mmHg for end-tidal CO_2 guidance seems reasonable during prehospital care. Particularly, end-tidal partial pressures of less than 35 mmHg were associated with a significantly increased mortality.

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Impact factor: 38.9 ; Q1

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2. Ibrutinib plus RICE or RVICI for relapsed/refractory mature B-cell non-Hodgkin lymphoma in children and young adults: SPARKLE trial
Burke GAA, Vinti L, Kabickova E, Beishuizen A, Tacyildiz N, Uyttebroeck A, Kang HJ, Luisi F, Minard-Colin V, Burkhardt B, Tamegnon M, Sun S, Curtis M, Deshpande S, Nottage K, Howes A, Srinivasan S, Bhojwani D, Norris R, Cairo M.

Part 1 results of the open-label, randomized, global phase 3 SPARKLE trial supported continued assessment of ibrutinib with either modified rituximab, ifosfamide, carboplatin, and etoposide (RICE) or rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone (RVICI) in pediatric patients with relapsed/refractory (R/R) mature B-cell non-Hodgkin lymphoma (B-NHL). We report final results of Part 2 evaluating the efficacy of ibrutinib plus RICE or RVICI vs RICE/RVICI alone. Patients aged 1 to 30 years (initial diagnosis <18 years) were randomized 2:1 to receive ibrutinib with or without RICE/RVICI. Primary endpoint was event-free survival (EFS) based on independent committee-confirmed events. Fifty-one patients were enrolled. Median age was 15 years; Burkitt lymphoma, Burkitt leukemia, and Burkitt-like lymphoma (total: 45%) and diffuse large B-cell lymphoma/primary mediastinal B-cell lymphoma (51%) were the most common subtypes. At the preplanned interim analysis, median EFS was 6.1 vs 7.0 months with ibrutinib plus RICE/RVICI vs RICE/RVICI, respectively (hazard ratio, 0.9; 90% confidence interval, 0.5-1.6; P = .387); further enrollment was ceased. With ibrutinib plus RICE/RVICI vs RICE/RVICI, median overall survival was 14.1

vs 11.1 months, overall response rate was 69% vs 81%, and 46% vs 44% proceeded to stem cell transplantation. In both treatment arms, 100% of patients experienced grade ≥3 treatment-emergent adverse events. No EFS benefit was seen with ibrutinib. Salvage was generally poor in patients who received prior rituximab, regardless of treatment arm. No new safety signals were observed. Ibrutinib exposure in pediatric patients fell within the target range of exposure in adults. Trial is registered on www.clinicaltrials.gov (NCT02703272).

Gepubliceerd: Blood Adv. 2023;7(4):602-10.
Impact factor: 7.6 ; Q1

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3. Implementation of Recommendations on the Use of Corticosteroids in Severe COVID-19
Camirand-Lemyre F, Merson L, Tirupakuzhi Vijayaraghavan BK, Burrell AJC, Citarella BW, Domingue MP, Lévesque S, Usuf E, Wils EJ, Ohshimo S, Martin-Loeches I, Sandulescu O, Laake JH, Lamontagne F, ISARIC Clinical Characterisation 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.

Importance: Research diversity and representativeness are paramount in building trust, generating valid biomedical knowledge, and possibly in implementing clinical guidelines.
Objectives: To compare variations over time and across World Health Organization (WHO) geographic regions of corticosteroid use for treatment of severe COVID-19; secondary objectives were to evaluate the association between the timing of publication of the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial (June 2020) and the WHO guidelines for corticosteroids (September 2020) and the temporal trends observed in corticosteroid use by region and to describe the geographic distribution of the recruitment in clinical trials that informed the WHO recommendation.
Design, setting, and participants: This prospective cohort study of 434 851 patients was conducted between January 31, 2020, and September 2, 2022, in 63 countries worldwide. The data were collected under the auspices of the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC)-WHO Clinical Characterisation Protocol for Severe Emerging Infections. Analyses were restricted to patients hospitalized for severe COVID-19 (a subset of the ISARIC data set).
Exposure: Corticosteroid use as reported to the ISARIC-WHO Clinical Characterisation Protocol for Severe Emerging Infections.
Main outcomes and measures: Number and percentage of patients hospitalized with severe COVID-19 who received corticosteroids by time period and by WHO geographic region.
Results: Among 434 851 patients with confirmed severe or critical COVID-19 for whom receipt of corticosteroids could be ascertained (median [IQR] age, 61.0 [48.0-74.0] years; 53.0% male), 174 307 (40.1%) received corticosteroids during the study period. Of the participants in clinical trials that informed the guideline, 91.6% were recruited from the United Kingdom. In all regions, corticosteroid use for severe COVID-19 increased, but this increase corresponded to the timing of the RECOVERY trial (time-interruption coefficient 1.0 [95% CI, 0.9-1.2]) and WHO guideline (time-interruption coefficient 1.9 [95% CI, 1.7-2.0]) publications only in Europe. At the end of the study period, corticosteroid use for treatment of severe COVID-19 was highest in the Americas (5421 of 6095 [88.9%]; 95% CI, 87.7-90.2) and lowest in Africa (31 588 of 185 191 [17.1%]; 95% CI, 16.8-17.3).
Conclusions and relevance: The results of this cohort study showed that implementation of the guidelines for use of corticosteroids in the treatment of severe COVID-19 varied geographically. Uptake of corticosteroid treatment was lower in regions with limited clinical trial involvement. Improving research diversity and representativeness may facilitate timely knowledge uptake and guideline implementation.

Gepubliceerd: JAMA Netw Open. 2023;6(12):e2346502.
Impact factor: 13.8 ; Q1

4. Neurological manifestations of COVID-19 in adults and children
Cho SM, White N, Premraj L, Battaglini D, Fanning J, Suen J, Bassi GL, Fraser J, Robba C, Griffee M, Singh B, Citarella BW, Merson L, Solomon T, Thomson D, ISARIC Clinical Characterisation 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.

Different neurological manifestations of coronavirus disease 2019 (COVID-19) in adults and children and their impact have not been well characterized. We aimed to determine the prevalence of neurological manifestations and in-hospital complications among hospitalized COVID-19 patients and ascertain differences between adults and children. We conducted a prospective multicentre observational study using the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) cohort across 1507 sites worldwide from 30 January 2020 to 25 May 2021. Analyses of neurological manifestations and neurological complications considered unadjusted prevalence estimates for predefined patient subgroups, and adjusted estimates as a function of patient age and time of hospitalization using generalized linear models. Overall, 161 239 patients (158 267 adults; 2972 children) hospitalized with COVID-19 and assessed for neurological manifestations and complications were included. In adults and children, the most frequent neurological manifestations at admission were fatigue (adults: 37.4%; children: 20.4%), altered consciousness (20.9%; 6.8%), myalgia (16.9%; 7.6%), dysgeusia (7.4%; 1.9%), anosmia (6.0%; 2.2%) and seizure (1.1%; 5.2%). In adults, the most frequent in-hospital neurological complications were stroke (1.5%), seizure (1%) and CNS infection (0.2%). Each occurred more frequently in intensive care unit (ICU) than in non-ICU patients. In children, seizure was the only neurological complication to occur more frequently in ICU versus non-ICU (7.1% versus 2.3%, $P < 0.001$). Stroke prevalence increased with increasing age, while CNS infection and seizure steadily decreased with age. There was a dramatic decrease in stroke over time during the pandemic. Hypertension, chronic neurological disease and the use of extracorporeal membrane oxygenation were associated with increased risk of stroke. Altered consciousness was associated with CNS infection, seizure and stroke. All in-hospital neurological complications were associated with increased odds of death. The likelihood of death rose with increasing age, especially after 25 years of age. In conclusion, adults and children have different neurological manifestations and in-hospital complications associated with COVID-19. Stroke risk increased with increasing age, while CNS infection and seizure risk decreased with age.

Gepubliceerd: Brain. 2023;146(4):1648-61.
Impact factor: 14.5 ; Q1

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5. Risk factors of extubation failure in neurocritical patients with the most impaired consciousness
de Courson H, Massart N, Asehnoune K, Cinotti R, EINO Study group: Vermeijden JW, Cornet AD.

Gepubliceerd: Intensive Care Med. 2023;49(10):1251-3.
Impact factor: 38.9 ; Q1

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6. Age Moderates the Effect of Obesity on Mortality Risk in Critically Ill Patients With COVID-19: A Nationwide Observational Cohort Study
den Uil CA, Termorshuizen F, Rietdijk WJR, Sablerolles RSG, van der Kuy HPM, Haas LEM, van der Voort PHJ, de Lange DW, Pickkers P, de Keizer NF, Dutch COVID-19 Research Consortium: Silderhuis VM.

Objectives: A high body mass index (BMI) is associated with an unfavorable disease course in COVID-19, but not among those who require admission to the ICU. This has not been examined across different age groups. We examined whether age modifies the association between BMI and mortality among critically ill COVID-19 patients.
Design: An observational cohort study.
Setting: A nationwide registry analysis of critically ill patients with COVID-19 registered in the National Intensive Care Evaluation registry.
Patients: We included 15,701 critically ill patients with COVID-19 (10,768 males [68.6%] with median [interquartile range] age 64 yr [55-71 yr]), of whom 1,402 (8.9%) patients were less than 45 years.
Interventions: None.
Measurements and main results: In the total sample and after adjustment for age, gender, Acute Physiology and Chronic Health Evaluation IV, mechanical ventilation, and use of vasoactive drugs, we found that a BMI greater than or equal to 30 kg/m 2 does not affect hospital mortality (adjusted odds ratio [OR adj] = 0.98; 95% CI, 0.90-1.06; p = 0.62). For patients less than 45 years old, but not for those greater than or equal to 45 years old, a BMI greater than or equal to 30 kg/m 2 was associated with a lower hospital mortality (OR adj = 0.59; 95% CI, 0.36-0.96; p = 0.03).
Conclusions: A higher BMI may be favorably associated with a lower mortality among those less than 45 years old. This is in line with the so-called "obesity paradox" that was established for other groups of critically ill patients in broad age ranges. Further research is needed to understand this favorable association in young critically ill patients with COVID-19.

Gepubliceerd: Crit Care Med. 2023;51(4):484-91.
Impact factor: 8.8 ; Q1

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7. DeltaScan for the Assessment of Acute Encephalopathy and Delirium in ICU and non-ICU Patients, a Prospective Cross-Sectional Multicenter Validation Study
Ditzel FL, Hut SCA, van den Boogaard M, Boonstra M, Leijten FSS, Wils EJ, van Nesselrooij T, Kromkamp M, Rood PJT, Röder C, Bouvy PF, Coesmans M, Osse RJ, Pop-Purceleanu M, van Dellen E, Krulder JWM, Milisen K, Faaij R, Vondeling AM, Kamper AM, van Munster BC, de Jonghe A, Winters MAM, van der Ploeg J, van der Zwaag S, Koek DHL, Drenth-van Maanen CAC, Beishuizen A, van den Bos DM, Cahn W, Schuit E, Slooter AJC.

Objectives: To measure the diagnostic accuracy of DeltaScan: a portable real-time brain state monitor for identifying delirium, a manifestation of acute encephalopathy (AE) detectable by polymorphic delta activity (PDA) in single-channel electroencephalograms (EEGs).
Design: Prospective cross-sectional study.
Setting: Six Intensive Care Units (ICU's) and 17 non-ICU departments, including a psychiatric department across 10 Dutch hospitals.
Participants: 494 patients, median age 75 (IQR:64-87), 53% male, 46% in ICUs, 29% delirious.
Measurements: DeltaScan recorded 4-minute EEGs, using an algorithm to select the first 96 seconds of artifact-free data for PDA detection. This algorithm was trained and calibrated on two independent datasets.
Methods: Initial validation of the algorithm for AE involved comparing its output with an expert EEG panel's visual inspection. The primary objective was to assess DeltaScan's accuracy in identifying delirium against a delirium expert panel's consensus.
Results: DeltaScan had a 99% success rate, rejecting 6 of the 494 EEG's due to artifacts. Performance showed and an Area Under the Receiver Operating Characteristic Curve (AUC) of 0.86 (95% CI: 0.83-0.90) for AE (sensitivity: 0.75, 95%CI=0.68-0.81, specificity: 0.87 95%CI=0.83-0.91. The AUC was 0.71 for delirium (95%CI=0.66-0.75, sensitivity: 0.61 95%CI=0.52-0.69, specificity: 72, 95%CI=0.67-0.77). Our validation aim was an NPV for delirium above 0.80 which proved to be 0.82 (95%CI: 0.77-0.86).

Among 84 non-delirious psychiatric patients, DeltaScan differentiated delirium from other disorders with a 94% (95%CI: 87-98%) specificity.
Conclusions: DeltaScan can diagnose AE at bedside and shows a clear relationship with clinical delirium. Further research is required to explore its role in predicting delirium-related outcomes.

Gepubliceerd: Am J Geriatr Psychiatry. 2023.
Impact factor: 7.2 ; Q1

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8. Thrombotic and hemorrhagic complications of COVID-19 in adults hospitalized in high-income countries compared with those in adults hospitalized in low- and middle-income countries in an international registry
Griffee MJ, Bozza PT, Reyes LF, Eddington DP, Rosenberger D, Merson L, Citarella BW, Fanning JP, Alexander PMA, Fraser J, Dalton H, Cho SM, ISARIC Clinical Characterisation 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: COVID-19 has been associated with a broad range of thromboembolic, ischemic, and hemorrhagic complications (coagulopathy complications). Most studies have focused on patients with severe disease from high-income countries (HICs).
Objectives: The main aims were to compare the frequency of coagulopathy complications in developing countries (low- and middle-income countries [LMICs]) with those in HICs, delineate the frequency across a range of treatment levels, and determine associations with in-hospital mortality.
Methods: Adult patients enrolled in an observational, multinational registry, the International Severe Acute Respiratory and Emerging Infections COVID-19 study, between January 1, 2020, and September 15, 2021, met inclusion criteria, including admission to a hospital for laboratory-confirmed, acute COVID-19 and data on complications and survival. The advanced-treatment cohort received care, such as admission to the intensive care unit, mechanical ventilation, or inotropes or vasopressors; the basic-treatment cohort did not receive any of these interventions.
Results: The study population included 495,682 patients from 52 countries, with 63% from LMICs and 85% in the basic treatment cohort. The frequency of coagulopathy complications was higher in HICs (0.76%-3.4%) than in LMICs (0.09%-1.22%). Complications were more frequent in the advanced-treatment cohort than in the basic-treatment cohort. Coagulopathy complications were associated with increased in-hospital mortality (odds ratio, 1.58; 95% CI, 1.52-1.64). The increased mortality associated with these complications was higher in LMICs (58.5%) than in HICs (35.4%). After controlling for coagulopathy complications, treatment intensity, and multiple other factors, the mortality was higher among patients in LMICs than among patients in HICs (odds ratio, 1.45; 95% CI, 1.39-1.51).
Conclusion: In a large, international registry of patients hospitalized for COVID-19, coagulopathy complications were more frequent in HICs than in LMICs (developing countries). Increased mortality associated with coagulopathy complications was of a greater magnitude among patients in LMICs. Additional research is needed regarding timely diagnosis of and intervention for coagulation derangements associated with COVID-19, particularly for limited-resource settings.

Gepubliceerd: Res Pract Thromb Haemost. 2023;7(5):102142.
Impact factor: 4.6 ; Q2

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9. Characteristics and outcomes of an international cohort of 600 000 hospitalized patients with COVID-19

Kartsonaki C, Baillie JK, Barrio NG, Baruch J, Beane A, Blumberg L, Bozza F, Broadley T, Burrell A, Carson G, Citarella BW, Dagens A, Dankwa EA, Donnelly CA, Dunning J, Elotmani L, Escher M, Farshait N, Goffard JC, Gonçalves BP, Hall M, Hashmi M, Sim Lim Heng B, Ho A, Jassat W, Pedrera Jiménez M, Laouenan C, Lissauer S, Martin-Loeches I, Mentré F, Merson L, Morton B, Munblit D, Nekliudov NA, Nichol AD, Singh Oinam BC, Ong D, Panda PK, Petrovic M, Pritchard MG, Ramakrishnan N, Ramos GV, Roger C, Sandulescu O, Semple MG, Sharma P, Sigfrid L, Somers EC, Streinu-Cercel A, Taccone F, Vecham PK, Kumar Tirupakuzhi Vijayaraghavan B, Wei J, Wils EJ, Ci Wong X, Horby P, Rojek A, Olliaro PL, ISARIC Clinical Characterisation 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: We describe demographic features, treatments and clinical outcomes in the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) COVID-19 cohort, one of the world's largest international, standardized data sets concerning hospitalized patients.
Methods: The data set analysed includes COVID-19 patients hospitalized between January 2020 and January 2022 in 52 countries. We investigated how symptoms on admission, co-morbidities, risk factors and treatments varied by age, sex and other characteristics. We used Cox regression models to investigate associations between demographics, symptoms, co-morbidities and other factors with risk of death, admission to an intensive care unit (ICU) and invasive mechanical ventilation (IMV).
Results: Data were available for 689 572 patients with laboratory-confirmed (91.1%) or clinically diagnosed (8.9%) SARS-CoV-2 infection from 52 countries. Age [adjusted hazard ratio per 10 years 1.49 (95% CI 1.48, 1.49)] and male sex [1.23 (1.21, 1.24)] were associated with a higher risk of death. Rates of admission to an ICU and use of IMV increased with age up to age 60 years then dropped. Symptoms, co-morbidities and treatments varied by age and had varied associations with clinical outcomes. The case-fatality ratio varied by country partly due to differences in the clinical characteristics of recruited patients and was on average 21.5%.
Conclusions: Age was the strongest determinant of risk of death, with a ∼30-fold difference between the oldest and youngest groups; each of the co-morbidities included was associated with up to an almost 2-fold increase in risk. Smoking and obesity were also associated with a higher risk of death. The size of our international database and the standardized data collection method make this study a comprehensive international description of COVID-19 clinical features. Our findings may inform strategies that involve prioritization of patients hospitalized with COVID-19 who have a higher risk of death.

Gepubliceerd: Int J Epidemiol. 2023;52(2):355-76.
Impact factor: 7.7 ; Q1

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10. Early mobilisation in critically ill COVID-19 patients: a subanalysis of the ESICM-initiated UNITE-COVID observational study

Kloss P, Lindholz M, Milnik A, Azoulay E, Cecconi M, Citerio G, De Corte T, Duska F, Galarza L, Greco M, Girbes ARJ, Kesecioglu J, Mellinghoff J, Ostermann M, Pellegrini M, Teboul JL, De Waele J, Wong A, Schaller SJ, ESICM UNITE COVID Investigators: Beishuizen A, Cornet AD.

Background: Early mobilisation (EM) is an intervention that may improve the outcome of critically ill patients. There is limited data on EM in COVID-19 patients and its use during the first pandemic wave.
Methods: This is a pre-planned subanalysis of the ESICM UNITE-COVID, an international multicenter observational study involving critically ill COVID-19 patients in the ICU between February 15th and May 15th, 2020. We analysed variables associated with the initiation of EM (within 72 h of ICU admission) and explored the impact of EM on mortality, ICU and hospital length of stay, as well as discharge location. Statistical analyses were done using (generalised) linear mixed-effect models and ANOVAs.

Results: Mobilisation data from 4190 patients from 280 ICUs in 45 countries were analysed. 1114 (26.6%) of these patients received mobilisation within 72 h after ICU admission; 3076 (73.4%) did not. In our analysis of factors associated with EM, mechanical ventilation at admission (OR 0.29; 95% CI 0.25, 0.35; p = 0.001), higher age (OR 0.99; 95% CI 0.98, 1.00; p ≤ 0.001), pre-existing asthma (OR 0.84; 95% CI 0.73, 0.98; p = 0.028), and pre-existing kidney disease (OR 0.84; 95% CI 0.71, 0.99; p = 0.036) were negatively associated with the initiation of EM. EM was associated with a higher chance of being discharged home (OR 1.31; 95% CI 1.08, 1.58; p = 0.007) but was not associated with length of stay in ICU (adj. difference 0.91 days; 95% CI - 0.47, 1.37, p = 0.34) and hospital (adj. difference 1.4 days; 95% CI - 0.62, 2.35, p = 0.24) or mortality (OR 0.88; 95% CI 0.7, 1.09, p = 0.24) when adjusted for covariates.
Conclusions: Our findings demonstrate that a quarter of COVID-19 patients received EM. There was no association found between EM in COVID-19 patients' ICU and hospital length of stay or mortality. However, EM in COVID-19 patients was associated with increased odds of being discharged home rather than to a care facility. Trial registration ClinicalTrials.gov: NCT04836065(retrospectively registered April 8th 2021).

Gepubliceerd: Ann Intensive Care. 2023;13(1):112.
Impact factor: 8.1 ; Q1

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11. Pharmacokinetic analysis of vilobelimab, anaphylatoxin C5a and antidrug antibodies in PANAMO: a phase 3 study in critically ill, invasively mechanically ventilated COVID-19 patients
Lim EHT, Vlaar APJ, de Bruin S, Rückinger S, Thielert C, Habel M, Guo R, Burnett BP, Dickinson J, Brouwer MC, Riedemann NC, van de Beek D, PANAMO study group: Cornet AD.

BACKGROUND: Vilobelimab, a complement 5a (C5a)-specific monoclonal antibody, reduced mortality in critically ill COVID-19 patients in a phase 3 multicentre, randomized, double-blind, placebo-controlled study. As part of the study, vilobelimab concentrations and C5a levels as well as antidrug antibodies (ADAs) to vilobelimab were analysed. RESULTS: From Oct 1, 2020 to Oct 4, 2021, 368 invasively mechanically ventilated COVID-19 patients were randomized: 177 patients were randomly assigned to receive vilobelimab while 191 patients received placebo. Pharmacokinetic sampling was only performed at sites in Western Europe. Blood samples for vilobelimab measurements were available for 93 of 177 (53%) patients in the vilobelimab group and 99 of 191 (52%) patients in the placebo group. On day 8, after three infusions, mean vilobelimab (trough) concentrations ranged from 21,799.3 to 302,972.1 ng/mL (geometric mean 137,881.3 ng/mL). Blood samples for C5a measurements were available for 94 of 177 (53%) patients in the vilobelimab group and 99 of 191 (52%) patients in the placebo group. At screening, C5a levels were highly elevated and comparable between groups. In the vilobelimab group, median C5a levels were 118.3 ng/mL [IQR 71.2-168.2 ng/mL] and in the placebo group, median C5a levels were 104.6 ng/mL [IQR 77.5-156.6 ng/mL]. By day 8, median C5a levels were reduced by 87% in the vilobelimab group (median 14.5 ng/mL [IQR 9.5-21.0 ng/mL], p < 0.001) versus an 11% increase in the placebo group (median 119.2 ng/mL [IQR 85.9-152.1 ng/mL]). Beyond day 8, though plasma sampling was sparse, C5a levels did not reach screening levels in the vilobelimab group while C5a levels remained elevated in the placebo group. Treatment-emergent ADAs were observed in one patient in the vilobelimab group at hospital discharge on day 40 and in one patient in the placebo group at hospital discharge on day 25. CONCLUSIONS: This analysis shows that vilobelimab efficiently inhibits C5a in critically ill COVID-19 patients. There was no evidence of immunogenicity associated with vilobelimab treatment. Trial registration ClinicalTrials.gov, NCT04333420. Registered 3 April 2020, https://clinicaltrials.gov/ct2/show/NCT04333420.

Gepubliceerd: Intensive Care Med Exp. 2023;11(1):37.
Impact factor: 3.5 ; Q onbekend

12. Diabetes mellitus is associated with 90-day mortality in old critically ill COVID-19 patients: a multicenter prospective observational cohort study
Mayerhöfer T, Klein S, Wernly B, Flaatten H, Guidet B, De Lange DW, Fjølner J, Leaver S, Beil M, Sviri S, Bruno RR, Artigas A, van Heerden PV, Pinto BB, Schefold JC, Moreno R, Cecconi M, Szczeklik W, Jung C, Joannidis M, COVIP study group: Cornet AD.

Background: Several studies have found an association between diabetes mellitus, disease severity and outcome in COVID-19 patients. Old critically ill patients are particularly at risk. This study aimed to investigate the impact of diabetes mellitus on 90-day mortality in a high-risk cohort of critically ill patients over 70 years of age.
Methods: This multicentre international prospective cohort study was performed in 151 ICUs across 26 countries. We included patients ≥ 70 years of age with a confirmed SARS-CoV-2 infection admitted to the intensive care unit from 19th March 2020 through 15th July 2021. Patients were categorized into two groups according to the presence of diabetes mellitus. Primary outcome was 90-day mortality. Kaplan-Meier overall survival curves until day 90 were analysed and compared using the log-rank test. Mixed-effect Weibull regression models were computed to investigate the influence of diabetes mellitus on 90-day mortality.
Results: This study included 3420 patients with a median age of 76 years were included. Among these, 37.3% (n = 1277) had a history of diabetes mellitus. Patients with diabetes showed higher rates of frailty (32% vs. 18%) and several comorbidities including chronic heart failure (20% vs. 11%), hypertension (79% vs. 59%) and chronic kidney disease (25% vs. 11%), but not of pulmonary comorbidities (22% vs. 22%). The 90-day mortality was significantly higher in patients with diabetes than those without diabetes (64% vs. 56%, p < 0.001). The association of diabetes and 90-day mortality remained significant (HR 1.18 [1.06-1.31], p = 0.003) after adjustment for age, sex, SOFA-score and other comorbidities in a Weibull regression analysis.
Conclusion: Diabetes mellitus was a relevant risk factor for 90-day mortality in old critically ill patients with COVID-19.
Study registration: NCT04321265, registered March 19th, 2020.

Gepubliceerd: Infection. 2023;51(5):1407-15.
Impact factor: 7.5 ; Q1

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13. Myoclonus in comatose patients with electrographic status epilepticus after cardiac arrest: Corresponding EEG patterns, effects of treatment and outcomes
Nutma S, Ruijter BJ, Beishuizen A, Tromp SC, Scholten E, Horn J, van den Bergh WM, van Kranen-Mastenbroek VH, Thomeer EC, Moudrous W, Aries M, van Putten MJ, Hofmeijer J.

Objective: To clarify the significance of any form of myoclonus in comatose patients after cardiac arrest with rhythmic and periodic EEG patterns (RPPs) by analyzing associations between myoclonus and EEG pattern, response to anti-seizure medication and neurological outcome.
Design: Post hoc analysis of the prospective randomized Treatment of ELectroencephalographic STatus Epilepticus After Cardiopulmonary Resuscitation (TELSTAR) trial.
Setting: Eleven ICUs in the Netherlands and Belgium.
Patients: One hundred and fifty-seven adult comatose post-cardiac arrest patients with RPPs on continuous EEG monitoring.
Interventions: Anti-seizure medication vs no anti-seizure medication in addition to standard care.
Measurements and main results: Of 157 patients, 98 (63%) had myoclonus at inclusion. Myoclonus was not associated with one specific RPP type. However, myoclonus was associated with a smaller

probability of a continuous EEG background pattern (48% in patients with vs 75% without myoclonus, odds ratio (OR) 0.31; 95% confidence interval (CI) 0.16-0.64) and earlier onset of RPPs (24% vs 9% within 24 hours after cardiac arrest, OR 3.86;95% CI 1.64-9.11). Myoclonus was associated with poor outcome at three months, but not invariably so (poor neurological outcome in 96% vs 82%, p = 0.004). Anti-seizure medication did not improve outcome, regardless of myoclonus presence (6% good outcome in the intervention group vs 2% in the control group, OR 0.33; 95% CI 0.03-3.32).
Conclusions: Myoclonus in comatose patients after cardiac arrest with RPPs is associated with poor outcome and discontinuous or suppressed EEG. However, presence of myoclonus does not interact with the effects of anti-seizure medication and cannot predict a poor outcome without false positives.

Gepubliceerd: Resuscitation. 2023;186:109745.
Impact factor: 6.5 ; Q1

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14. A randomised trial of anti-GM-CSF otilimab in severe COVID-19 pneumonia (OSCAR)
Patel J, Bass D, Beishuizen A, Bocca Ruiz X, Boughanmi H, Cahn A, Colombo H, Criner GJ, Davy K, de-Miguel-Díez J, Doreski PA, Fernandes S, François B, Gupta A, Hanrott K, Hatlen T, Inman D, Isaacs JD, Jarvis E, Kostina N, Kropotina T, Lacherade JC, Lakshminarayanan D, Martinez-Ayala P, McEvoy C, Meziani F, Monchi M, Mukherjee S, Muñoz-Bermúdez R, Neisen J, O'Shea C, Plantefeve G, Schifano L, Schwab LE, Shahid Z, Shirano M, Smith JE, Sprinz E, Summers C, Terzi N, Tidswell MA, Trefilova Y, Williamson R, Wyncoll D, Layton M.

Background: Granulocyte-macrophage colony-stimulating factor (GM-CSF) and dysregulated myeloid cell responses are implicated in the pathophysiology and severity of COVID-19.
Methods: In this randomised, sequential, multicentre, placebo-controlled, double-blind study, adults aged 18-79 years (Part 1) or ≥70 years (Part 2) with severe COVID-19, respiratory failure and systemic inflammation (elevated C-reactive protein/ferritin) received a single intravenous infusion of otilimab 90 mg (human anti-GM-CSF monoclonal antibody) plus standard care (NCT04376684). The primary outcome was the proportion of patients alive and free of respiratory failure at Day 28.
Results: In Part 1 (n=806 randomised 1:1 otilimab:placebo), 71% of otilimab-treated patients were alive and free of respiratory failure at Day 28 *versus* 67% who received placebo; the model-adjusted difference of 5.3% was not statistically significant (95% CI -0.8-11.4%, p=0.09). A nominally significant model-adjusted difference of 19.1% (95% CI 5.2-33.1%, p=0.009) was observed in the predefined 70-79 years subgroup, but this was not confirmed in Part 2 (n=350 randomised) where the model-adjusted difference was 0.9% (95% CI -9.3-11.2%, p=0.86). Compared with placebo, otilimab resulted in lower serum concentrations of key inflammatory markers, including the putative pharmacodynamic biomarker CC chemokine ligand 17, indicative of GM-CSF pathway blockade. Adverse events were comparable between groups and consistent with severe COVID-19.
Conclusions: There was no significant difference in the proportion of patients alive and free of respiratory failure at Day 28. However, despite the lack of clinical benefit, a reduction in inflammatory markers was observed with otilimab, in addition to an acceptable safety profile.

Gepubliceerd: Eur Respir J. 2023;61(2).
Impact factor: 24.9 ; Q1

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15. Weaning from mechanical ventilation in intensive care units across 50 countries (WEAN SAFE): a multicentre, prospective, observational cohort study

Pham T, Heunks L, Bellani G, Madotto F, Aragao I, Beduneau G, Goligher EC, Grasselli G, Laake JH, Mancebo J, Peñuelas O, Piquilloud L, Pesenti A, Wunsch H, van Haren F, Brochard L, Laffey JG, WEAN SAFE Investigators: Vermeijden JW.

Background: Current management practices and outcomes in weaning from invasive mechanical ventilation are poorly understood. We aimed to describe the epidemiology, management, timings, risk for failure, and outcomes of weaning in patients requiring at least 2 days of invasive mechanical ventilation.
Methods: WEAN SAFE was an international, multicentre, prospective, observational cohort study done in 481 intensive care units in 50 countries. Eligible participants were older than 16 years, admitted to a participating intensive care unit, and receiving mechanical ventilation for 2 calendar days or longer. We defined weaning initiation as the first attempt to separate a patient from the ventilator, successful weaning as no reintubation or death within 7 days of extubation, and weaning eligibility criteria based on positive end-expiratory pressure, fractional concentration of oxygen in inspired air, and vasopressors. The primary outcome was the proportion of patients successfully weaned at 90 days. Key secondary outcomes included weaning duration, timing of weaning events, factors associated with weaning delay and weaning failure, and hospital outcomes. This study is registered with ClinicalTrials.gov, NCT03255109.
Findings: Between Oct 4, 2017, and June 25, 2018, 10 232 patients were screened for eligibility, of whom 5869 were enrolled. 4523 (77·1%) patients underwent at least one separation attempt and 3817 (65·0%) patients were successfully weaned from ventilation at day 90. 237 (4·0%) patients were transferred before any separation attempt, 153 (2·6%) were transferred after at least one separation attempt and not successfully weaned, and 1662 (28·3%) died while invasively ventilated. The median time from fulfilling weaning eligibility criteria to first separation attempt was 1 day (IQR 0-4), and 1013 (22·4%) patients had a delay in initiating first separation of 5 or more days. Of the 4523 (77·1%) patients with separation attempts, 2927 (64·7%) had a short wean (≤1 day), 457 (10·1%) had intermediate weaning (2-6 days), 433 (9·6%) required prolonged weaning (≥7 days), and 706 (15·6%) had weaning failure. Higher sedation scores were independently associated with delayed initiation of weaning. Delayed initiation of weaning and higher sedation scores were independently associated with weaning failure. 1742 (31·8%) of 5479 patients died in the intensive care unit and 2095 (38·3%) of 5465 patients died in hospital.
Interpretation: In critically ill patients receiving at least 2 days of invasive mechanical ventilation, only 65% were weaned at 90 days. A better understanding of factors that delay the weaning process, such as delays in weaning initiation or excessive sedation levels, might improve weaning success rates.

Gepubliceerd: Lancet Respir Med. 2023;11(5):465-76.
Impact factor: 76.2 ; Q1

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16. [Well-meant oxygen administration with harmful effects]
Saleh W, Cornet AD.

For more than hundred years oxygen has been administered to patients for a variety of indications: first and foremost to treat, and later to prevent, hypoxemia. Some years after the first exhilarating reports, it became apparent that hyperoxemia may have harmful sequelae. The pathophysiological mechanism has been determined: vasoconstiction of coronary, cerebral and systemic arteries. And additionally the formation of reactive oxygen species, resulting in cellular damage and ultimately cell death. In a variety of medical emergencies the detrimental clinical effects of hyperoxemia have been demonstrated: increased mortality and more organ dysfunction. And recently it was found the latter also applies to patients undergoing (elective) surgery. It might therefore be concluded that hyperoxemia is justifiable for short periods of time to prevent hypoxemia (i.e. endotracheal intubation), but in all other situations normoxemia should be the target.

Gepubliceerd: Ned Tijdschr Geneeskd. 2023;167.
Impact factor: onbekend

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17. Impact of reduced antibiotic treatment duration on antimicrobial resistance in critically ill patients in the randomized controlled SAPS-trial
Shajiei A, Berends MS, Luz CF, van Oers JA, Harmsen HJM, Vos P, Klont R, Loef BG, Reidinga AC, Bormans-Russell L, Linsen K, Dormans T, Otten M, van der Bij A, Beishuizen A, de Lange DW, de Jong E, Nijsten MW.

Background: In the previously reported SAPS trial (https://clinicaltrials.gov/ct2/show/NCT01139489), procalcitonin-guidance safely reduced the duration of antibiotic treatment in critically ill patients. We assessed the impact of shorter antibiotic treatment on antimicrobial resistance development in SAPS patients.
Materials and methods: Cultures were assessed for the presence of multi-drug resistant (MDR) or highly resistant organisms (HRMO) and compared between PCT-guided and control patients. Baseline isolates from 30 days before to 5 days after randomization were compared with those from 5 to 30 days post-randomization. The primary endpoint was the incidence of new MDR/HRMO positive patients.
Results: In total, 8,113 cultures with 96,515 antibiotic test results were evaluated for 439 and 482 patients randomized to the PCT and control groups, respectively. Disease severity at admission was similar for both groups. Median (IQR) durations of the first course of antibiotics were 6 days (4-10) and 7 days (5-11), respectively (p = 0.0001). Antibiotic-free days were 7 days (IQR 0-14) and 6 days (0-13; p = 0.05). Of all isolates assessed, 13% were MDR/HRMO positive and at baseline 186 (20%) patients were MDR/HMRO-positive. The incidence of new MDR/HRMO was 39 (8.9%) and 45 (9.3%) in PCT and control patients, respectively (p = 0.82). The time courses for MDR/HRMO development were also similar for both groups (p = 0.33).
Conclusions: In the 921 randomized patients studied, the small but statistically significant reduction in antibiotic treatment in the PCT-group did not translate into a detectable change in antimicrobial resistance. Studies with larger differences in antibiotic treatment duration, larger study populations or populations with higher MDR/HRMO incidences might detect such differences.

Gepubliceerd: Front Med (Lausanne). 2023;10:1080007.
Impact factor: 3.9 ; Q2

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18. Replacement Fibrosis in the Diaphragm of Mechanically Ventilated Critically Ill Patients
Shi Z, van den Berg M, Bogaards S, Conijn S, Paul M, Beishuizen A, Heunks L, Ottenheijm CAC.

Gepubliceerd: Am J Respir Crit Care Med. 2023;207(3):351-4.
Impact factor: 24.7 ; Q1

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19. Early EEG monitoring predicts clinical outcome in patients with moderate to severe traumatic brain injury
Tewarie PKB, Beernink TMJ, Eertman-Meyer CJ, Cornet AD, Beishuizen A, van Putten M, Tjepkema-Cloostermans MC.

There is a need for reliable predictors in patients with moderate to severe traumatic brain injury to assist clinical decision making. We assess the ability of early continuous EEG monitoring at the

intensive care unit (ICU) in patients with traumatic brain injury (TBI) to predict long term clinical outcome and evaluate its complementary value to current clinical standards. We performed continuous EEG measurements in patients with moderate to severe TBI during the first week of ICU admission. We assessed the Extended Glasgow Outcome Scale (GOSE) at 12 months, dichotomized into poor (GOSE 1-3) and good (GOSE 4-8) outcome. We extracted EEG spectral features, brain symmetry index, coherence, aperiodic exponent of the power spectrum, long range temporal correlations, and broken detailed balance. A random forest classifier using feature selection was trained to predict poor clinical outcome based on EEG features at 12, 24, 48, 72 and 96 h after trauma. We compared our predictor with the IMPACT score, the best available predictor, based on clinical, radiological and laboratory findings. In addition we created a combined model using EEG as well as the clinical, radiological and laboratory findings. We included hundred-seven patients. The best prediction model using EEG parameters was found at 72 h after trauma with an AUC of 0.82 (0.69-0.92), specificity of 0.83 (0.67-0.99) and sensitivity of 0.74 (0.63-0.93). The IMPACT score predicted poor outcome with an AUC of 0.81 (0.62-0.93), sensitivity of 0.86 (0.74-0.96) and specificity of 0.70 (0.43-0.83). A model using EEG and clinical, radiological and laboratory parameters resulted in a better prediction of poor outcome ($p < 0.001$) with an AUC of 0.89 (0.72-0.99), sensitivity of 0.83 (0.62-0.93) and specificity of 0.85 (0.75-1.00). EEG features have potential use for predicting clinical outcome and decision making in patients with moderate to severe TBI and provide complementary information to current clinical standards.

Gepubliceerd: Neuroimage Clin. 2023;37:103350.
Impact factor: 4.2 ; Q2

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20. Automated identification of patient subgroups: A case-study on mortality of COVID-19 patients admitted to the ICU
Vagliano I, Kingma MY, Dongelmans DA, de Lange DW, de Keizer NF, Schut MC, Dutch COVID-19 ICU Research Consortium: Silderhuis VM.

Background: - Subgroup discovery (SGD) is the automated splitting of the data into complex subgroups. Various SGD methods have been applied to the medical domain, but none have been extensively evaluated. We assess the numerical and clinical quality of SGD methods.
Method: - We applied the improved Subgroup Set Discovery (SSD++), Patient Rule Induction Method (PRIM) and APRIORI - Subgroup Discovery (APRIORI-SD) algorithms to obtain patient subgroups on observational data of 14,548 COVID-19 patients admitted to 73 Dutch intensive care units. Hospital mortality was the clinical outcome. Numerical significance of the subgroups was assessed with information-theoretic measures. Clinical significance of the subgroups was assessed by comparing variable importance on population and subgroup levels and by expert evaluation.
Results: - The tested algorithms varied widely in the total number of discovered subgroups (5-62), the number of selected variables, and the predictive value of the subgroups. Qualitative assessment showed that the found subgroups make clinical sense. SSD++ found most subgroups (n = 62), which added predictive value and generally showed high potential for clinical use. APRIORI-SD and PRIM found fewer subgroups (n = 5 and 6), which did not add predictive value and were clinically less relevant.
Conclusion: - Automated SGD methods find clinical subgroups that are relevant when assessed quantitatively (yield added predictive value) and qualitatively (intensivists consider the subgroups significant). Different methods yield different subgroups with varying degrees of predictive performance and clinical quality. External validation is needed to generalize the results to other populations and future research should explore which algorithm performs best in other settings.

Gepubliceerd: Comput Biol Med. 2023;163:107146.
Impact factor: 7.7 ; Q1

21. Conservative versus Liberal Oxygenation Targets in Intensive Care Unit Patients (ICONIC): A Randomized Clinical Trial

van der Wal LI, Grim CCA, Del Prado MR, van Westerloo DJ, Boerma EC, Rijnhart-de Jong HG, Reidinga AC, Loef BG, van der Heiden PLJ, Sigtermans MJ, Paulus F, Cornet AD, Loconte M, Schoonderbeek FJ, de Keizer NF, Bakhshi-Raiez F, Le Cessie S, Serpa Neto A, Pelosi P, Schultz MJ, Helmerhorst HJF, de Jonge E.

Rationale: Supplemental oxygen is widely administered to ICU patients, but appropriate oxygenation targets remain unclear.
Objectives: This study aimed to determine whether a low-oxygenation strategy would lower 28-day mortality compared with a high-oxygenation strategy.
Methods: This randomized multicenter trial included mechanically ventilated ICU patients with an expected ventilation duration of at least 24 hours. Patients were randomized 1:1 to a low-oxygenation (Pa_{O2}, 55-80 mm Hg; or oxygen saturation as measured by pulse oximetry, 91-94%) or high-oxygenation (Pa_{O2}, 110-150 mm Hg; or oxygen saturation as measured by pulse oximetry, 96-100%) target until ICU discharge or 28 days after randomization, whichever came first. The primary outcome was 28-day mortality. The study was stopped prematurely because of the COVID-19 pandemic when 664 of the planned 1,512 patients were included.
Measurements and Main Results: Between November 2018 and November 2021, a total of 664 patients were included in the trial: 335 in the low-oxygenation group and 329 in the high-oxygenation group. The median achieved Pa_{O2} was 75 mm Hg (interquartile range, 70-84) and 115 mm Hg (interquartile range, 100-129) in the low- and high-oxygenation groups, respectively. At Day 28, 129 (38.5%) and 114 (34.7%) patients had died in the low- and high-oxygenation groups, respectively (risk ratio, 1.11; 95% confidence interval, 0.9-1.4; *P* = 0.30). At least one serious adverse event was reported in 12 (3.6%) and 17 (5.2%) patients in the low- and high-oxygenation groups, respectively.
Conclusions: Among mechanically ventilated ICU patients with an expected mechanical ventilation duration of at least 24 hours, using a low-oxygenation strategy did not result in a reduction of 28-day mortality compared with a high-oxygenation strategy. Clinical trial registered with the National Trial Register and the International Clinical Trials Registry Platform (NTR7376).

Gepubliceerd: Am J Respir Crit Care Med. 2023;208(7):770-9.
Impact factor: 24.7 ; Q1

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22. Incidence, risk factors and pre-emptive screening for COVID-19 associated pulmonary aspergillosis in an era of immunomodulant therapy

van Grootveld R, van der Beek MT, Janssen NAF, Ergün M, van Dijk K, Bethlehem C, Stads S, van Paassen J, Heunks LMA, Bouman CSC, Reijers MHE, Brüggeman RJ, van de Veerdonk FL, van Bree SHW, van den Berg C, Kuindersma M, Wauters J, Beishuizen A, Verweij PE, Schouten JA.

Purpose: COVID-19 associated pulmonary aspergillosis (CAPA) is associated with increased morbidity and mortality in ICU patients. We investigated the incidence of, risk factors for and potential benefit of a pre-emptive screening strategy for CAPA in ICUs in the Netherlands/Belgium during immunosuppressive COVID-19 treatment.
Materials and methods: A retrospective, observational, multicentre study was performed from September 2020-April 2021 including patients admitted to the ICU who had undergone diagnostics for CAPA. Patients were classified based on 2020 ECMM/ISHAM consensus criteria.
Results: CAPA was diagnosed in 295/1977 (14.9%) patients. Corticosteroids were administered to 97.1% of patients and interleukin-6 inhibitors (anti-IL-6) to 23.5%. EORTC/MSGERC host factors or

treatment with anti-IL-6 with or without corticosteroids were not risk factors for CAPA. Ninety-day mortality was 65.3% (145/222) in patients with CAPA compared to 53.7% (176/328) without CAPA (p = 0.008). Median time from ICU admission to CAPA diagnosis was 12 days. Pre-emptive screening for CAPA was not associated with earlier diagnosis or reduced mortality compared to a reactive diagnostic strategy.
Conclusions: CAPA is an indicator of a protracted course of a COVID-19 infection. No benefit of pre-emptive screening was observed, but prospective studies comparing pre-defined strategies would be required to confirm this observation.

Gepubliceerd: J Crit Care. 2023;76:154272.
Impact factor: 3.7 ; Q2

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23. Utilization of mechanical power and associations with clinical outcomes in brain injured patients: a secondary analysis of the extubation strategies in neuro-intensive care unit patients and associations with outcome (ENIO) trial
Wahlster S, Sharma M, Taran S, Town JA, Stevens RD, Cinotti R, Asehoune K, Pelosi P, Robba C, ENIO Study Group Collaborators: Vermeijden JW, Cornet AD.

Background: There is insufficient evidence to guide ventilatory targets in acute brain injury (ABI). Recent studies have shown associations between mechanical power (MP) and mortality in critical care populations. We aimed to describe MP in ventilated patients with ABI, and evaluate associations between MP and clinical outcomes.
Methods: In this preplanned, secondary analysis of a prospective, multi-center, observational cohort study (ENIO, NCT03400904), we included adult patients with ABI (Glasgow Coma Scale ≤ 12 before intubation) who required mechanical ventilation (MV) ≥ 24 h. Using multivariable log binomial regressions, we separately assessed associations between MP on hospital day (HD)1, HD3, HD7 and clinical outcomes: hospital mortality, need for reintubation, tracheostomy placement, and development of acute respiratory distress syndrome (ARDS).
Results: We included 1217 patients (mean age 51.2 years [SD 18.1], 66% male, mean body mass index [BMI] 26.3 [SD 5.18]) hospitalized at 62 intensive care units in 18 countries. Hospital mortality was 11% (n = 139), 44% (n = 536) were extubated by HD7 of which 20% (107/536) required reintubation, 28% (n = 340) underwent tracheostomy placement, and 9% (n = 114) developed ARDS. The median MP on HD1, HD3, and HD7 was 11.9 J/min [IQR 9.2-15.1], 13 J/min [IQR 10-17], and 14 J/min [IQR 11-20], respectively. MP was overall higher in patients with ARDS, especially those with higher ARDS severity. After controlling for same-day pressure of arterial oxygen/fraction of inspired oxygen (P/F ratio), BMI, and neurological severity, MP at HD1, HD3, and HD7 was independently associated with hospital mortality, reintubation and tracheostomy placement. The adjusted relative risk (aRR) was greater at higher MP, and strongest for: mortality on HD1 (compared to the HD1 median MP 11.9 J/min, aRR at 17 J/min was 1.22, 95% CI 1.14-1.30) and HD3 (1.38, 95% CI 1.23-1.53), reintubation on HD1 (1.64; 95% CI 1.57-1.72), and tracheostomy on HD7 (1.53; 95%CI 1.18-1.99). MP was associated with the development of moderate-severe ARDS on HD1 (2.07; 95% CI 1.56-2.78) and HD3 (1.76; 95% CI 1.41-2.22).
Conclusions: Exposure to high MP during the first week of MV is associated with poor clinical outcomes in ABI, independent of P/F ratio and neurological severity. Potential benefits of optimizing ventilator settings to limit MP warrant further investigation.

Gepubliceerd: Crit Care. 2023;27(1):156.
Impact factor: 15.1 ; Q1

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24. Association of Country Income Level With the Characteristics and Outcomes of Critically Ill Patients Hospitalized With Acute Kidney Injury and COVID-19
Wainstein M, Spyrison N, Dai D, Ghadimi M, Chávez-Iñiguez JS, Rizo-Topete L, Citarella BW, Merson L, Pole JD, Claure-Del Granado R, Johnson DW, Shrapnel S, ISARIC Clinical Characterisation 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.

Introduction: Acute kidney injury (AKI) has been identified as one of the most common and significant problems in hospitalized patients with COVID-19. However, studies examining the relationship between COVID-19 and AKI in low- and low-middle income countries (LLMIC) are lacking. Given that AKI is known to carry a higher mortality rate in these countries, it is important to understand differences in this population.
Methods: This prospective, observational study examines the AKI incidence and characteristics of 32,210 patients with COVID-19 from 49 countries across all income levels who were admitted to an intensive care unit during their hospital stay.
Results: Among patients with COVID-19 admitted to the intensive care unit, AKI incidence was highest in patients in LLMIC, followed by patients in upper-middle income countries (UMIC) and high-income countries (HIC) (53%, 38%, and 30%, respectively), whereas dialysis rates were lowest among patients with AKI from LLMIC and highest among those from HIC (27% vs. 45%). Patients with AKI in LLMIC had the largest proportion of community-acquired AKI (CA-AKI) and highest rate of in-hospital death (79% vs. 54% in HIC and 66% in UMIC). The association between AKI, being from LLMIC and in-hospital death persisted even after adjusting for disease severity.
Conclusions: AKI is a particularly devastating complication of COVID-19 among patients from poorer nations where the gaps in accessibility and quality of healthcare delivery have a major impact on patient outcomes.

Gepubliceerd: Kidney Int Rep. 2023;8(8):1514-30.
Impact factor: 6.0 ; Q1

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25. Computational physiological models for individualised mechanical ventilation: a systematic literature review focussing on quality, availability, and clinical readiness
Warnaar RSP, Mulder MP, Fresiello L, Cornet AD, Heunks LMA, Donker DW, Oppersma E.

Background: Individualised optimisation of mechanical ventilation (MV) remains cumbersome in modern intensive care medicine. Computerised, model-based support systems could help in tailoring MV settings to the complex interactions between MV and the individual patient's pathophysiology. Therefore, we critically appraised the current literature on computational physiological models (CPMs) for individualised MV in the ICU with a focus on quality, availability, and clinical readiness.
Methods: A systematic literature search was conducted on 13 February 2023 in MEDLINE ALL, Embase, Scopus and Web of Science to identify original research articles describing CPMs for individualised MV in the ICU. The modelled physiological phenomena, clinical applications, and level of readiness were extracted. The quality of model design reporting and validation was assessed based on American Society of Mechanical Engineers (ASME) standards.
Results: Out of 6,333 unique publications, 149 publications were included. CPMs emerged since the 1970s with increasing levels of readiness. A total of 131 articles (88%) modelled lung mechanics, mainly for lung-protective ventilation. Gas exchange (n = 38, 26%) and gas homeostasis (n = 36, 24%) models had mainly applications in controlling oxygenation and ventilation. Respiratory muscle function models for diaphragm-protective ventilation emerged recently (n = 3, 2%). Three randomised controlled trials were initiated, applying the Beacon and CURE Soft models for gas exchange and PEEP optimisation. Overall, model design and quality were reported unsatisfactory in 93% and 21% of the articles, respectively.

Conclusion: CPMs are advancing towards clinical application as an explainable tool to optimise individualised MV. To promote clinical application, dedicated standards for quality assessment and model reporting are essential. Trial registration number PROSPERO- CRD42022301715 . Registered 05 February, 2022.

Gepubliceerd: Crit Care. 2023;27(1):268.
Impact factor: 15.1 ; Q1

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26. The clinical frailty scale, but not the FRAIL checklist is associated with mortality in old critically ill patients with COVID-19
Wernly B, Flaatten H, Leaver S, Guidet B, Jung C, COVIP investigators: Cornet AD.

Gepubliceerd: Crit Care. 2023;27(1):101.
Impact factor: 15.1 ; Q1

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27. Improving frailty assessment: the task is not finished
Wernly B, Flaatten H, Leaver S, Guidet B, Jung C, COVIP investigators: Cornet AD.

Gepubliceerd: Crit Care. 2023;27(1):218.
Impact factor: 15.1 ; Q1

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28. Acute kidney injury associated with nephrotoxic drugs in critically ill patients: a multicenter cohort study using electronic health record data
Yasrebi-de Kom IAR, Dongelmans DA, Abu-Hanna A, Schut MC, de Lange DW, van Roon EN, de Jonge E, Bouman CSC, de Keizer NF, Jager KJ, Klopotowska JE, RESCUE Study Group: Beishuizen A, Vermeijden JW, Masselink JB.

Background: Nephrotoxic drugs frequently cause acute kidney injury (AKI) in adult intensive care unit (ICU) patients. However, there is a lack of large pharmaco-epidemiological studies investigating the associations between drugs and AKI. Importantly, AKI risk factors may also be indications or contraindications for drugs and thereby confound the associations. Here, we aimed to estimate the associations between commonly administered (potentially) nephrotoxic drug groups and AKI in adult ICU patients whilst adjusting for confounding.
Methods: In this multicenter retrospective observational study, we included adult ICU admissions to 13 Dutch ICUs. We measured exposure to 44 predefined (potentially) nephrotoxic drug groups. The outcome was AKI during ICU admission. The association between each drug group and AKI was estimated using etiological cause-specific Cox proportional hazard models and adjusted for confounding. To facilitate an (independent) informed assessment of residual confounding, we manually identified drug group-specific confounders using a large drug knowledge database and existing literature.
Results: We included 92 616 ICU admissions, of which 13 492 developed AKI (15%). We found 14 drug groups to be associated with a higher hazard of AKI after adjustment for confounding. These groups included established (e.g. aminoglycosides), less well established (e.g. opioids) and controversial (e.g. sympathomimetics with α- and β-effect) drugs.
Conclusions: The results confirm existing insights and provide new ones regarding drug associated AKI in adult ICU patients. These insights warrant caution and extra monitoring when prescribing nephrotoxic drugs in the ICU and indicate which drug groups require further investigation.

Gepubliceerd: Clin Kidney J. 2023;16(12):2549-58.
Impact factor: 4.6 ; Q1

Totale impact factor: 408.6
Gemiddelde impact factor: 14.6

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: NVT (onbekend)
Gemiddelde impact factor: NVT

Interne geneeskunde

1. Compas-Y: A mixed methods pilot evaluation of a mobile self-compassion training for people with newly diagnosed cancer
Austin J, Schroevers MJ, Van Dijk J, Sanderman R, Børøsund E, Wymenga AMN, Bohlmeijer ET, Drossaert CHC.

Objective: Compas-Y is a compassionate mind training app that was co-designed to be fully adapted to mobile technology and to people with newly diagnosed cancer. This study aimed to evaluate the use, appreciation and impact of the app.
Methods: Seventy-one people with cancer who created an app account were included (38% breast cancer, 72% diagnosed <4 months ago, 76% received chemotherapy). Participants had very high baseline scores of self-compassion. In a convergent mixed methods design, back-end log-data (*n* = 71), pre-post surveys (*n* = 34) and semi-structured interviews (*n* = 23) collected for >8 weeks and were concurrently analysed using joint displays.
Results: About half of the participants (45%) used 4 of the 6 modules. Compas-Y was highly appreciated, with all content considered relevant and a source of support. Experienced benefits related to improved mental health. Particularly, we found significant changes in anxiety, but not in depression or well-being. In the interviews, people reported experiencing more rest and more positive emotions due to using the app. Process benefits included significant reductions in self-criticism (inadequate self and self-blame), but not self-compassion. In the interviews, people reported improved self-compassion and less self-criticism, more self-awareness, recognition and support, and improved emotion regulation and coping. The surveys did not capture the full range of outcomes that participants reported in the interviews.
Conclusions: Compas-Y is a highly appreciated mobile intervention that supported users in aspects of their mental health. Findings are discussed in terms of reach and adherence, app functionalities, co-design and tailoring of cancer-related and compassion-based eHealth.

Gepubliceerd: Digit Health. 2023;9:20552076231205272.
Impact factor: 3.9 ; Q1

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2. Is a History of Optimal Staging by Sentinel Lymph Node Biopsy in the Era Prior to Adjuvant Therapy Associated with Improved Outcome Once Melanoma Patients have Progressed to Advanced Disease?
Blankenstein SA, Bonenkamp JJ, Aarts MJB, van den Berkmortel F, Blank CU, Blokx WAM, Boers-Sonderen MJ, van den Eertwegh AJM, Franken MG, de Groot JWB, Haanen J, Hospers GAP, Kapiteijn EW, van Not OJ, Piersma D, van Rijn RS, Suijkerbuijk KPM, van der Veldt AAM, Vreugdenhil G, Westgeest HM, Wouters M, van Akkooi ACJ.

Introduction: Sentinel lymph node biopsy (SLNB) is important for staging in patients with primary cutaneous melanoma. Did having previously undergone SLNB also affect outcomes in patients once they have progressed to metastatic melanoma in the era prior to adjuvant therapy?
Methods: Data were retrieved from the Dutch Melanoma Treatment Registry, a prospectively collected, nationwide database of patients with unresectable stage IIIC or IV (advanced) melanoma between 2012 and 2018. Melanoma-specific survival (MSS) was compared between patients with advanced cutaneous melanoma, previously treated with a wide local excision (WLE) or WLE combined with SLNB as initial treatment of their primary tumor. Cox regression analyses were used to analyze the influence of different variables on MSS.
Results: In total, 2581 patients were included, of whom 1412 were treated with a WLE of the primary tumor alone and 1169 in whom this was combined with SLNB. At a median follow-up of 44 months

from diagnosis of advanced melanoma, MSS was significantly longer in patients who had previously undergone SLNB {median 23 months (95% confidence interval [CI] 19-29) vs. 18 months (95% CI 15-20) for patients treated with WLE alone; p = 0.002}. However, multivariate Cox regression did not identify SLNB as an independent favorable prognostic factor for MSS after diagnosis of advanced melanoma.
Conclusion: Prior to the availability of adjuvant systemic therapy, once patients have unresectable stage IIIC or IV (advanced) melanoma, there was no difference in disease outcome for patients who were or were not previously staged with SLNB.

Gepubliceerd: Ann Surg Oncol. 2023;30(1):573-86.
Impact factor: 3.7 ; Q1

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3. Differences in mental health status during the COVID-19 pandemic between patients undergoing in-center hemodialysis and peritoneal dialysis
Bouwmans P, Skalli Z, Vernooij RWM, Hemmelder MH, Konijn WS, Lips J, Mulder J, Bonenkamp AA, van Jaarsveld BC, Abrahams AC, DOMESTICO study group: Wijering RMJ.

Background: The mental health of dialysis patients during the COVID-19 pandemic may have been modulated by dialysis modality. Studies comparing mental health of in-center hemodialysis and peritoneal dialysis patients during the first 2 years of the pandemic are lacking.
Methods: We conducted repeated cross-sectional and multivariable regression analyses to compare the mental health of in-center hemodialysis and peritoneal dialysis patients from March 2019 until August 2021 using data from the Dutch nOcturnal and hoME dialysis Study To Improve Clinical Outcomes. The study period was divided into one pre-pandemic and six 3-month pandemic periods (period 1-period 6). Mental health was assessed with the Mental Component Summary score of the 12-item Short Form health survey and mental symptoms of the Dialysis Symptom Index.
Results: We included 1274 patients (968 on in-center hemodialysis and 306 on peritoneal dialysis). Mental Component Summary scores did not differ between in-center hemodialysis and peritoneal dialysis patients. In contrast, in-center hemodialysis patients more often reported nervousness during period 3 (27% vs 15%, P = 0.04), irritability and anxiety during period 3 (31% vs 18%, P = 0.03, 26% vs. 9%, P = 0.002, respectively) and period 4 (34% vs 22%, P = 0.04, 22% vs 11%, P = 0.03, respectively), and sadness in period 4 (38% vs 26%, P = 0.04) and period 5 (37% vs 22%, P = 0.009). Dialysis modality was independently associated with mental symptoms.
Conclusions: In-center hemodialysis patients more often experienced mental symptoms compared to peritoneal dialysis patients from September 2020 to June 2021, which corresponds to the second lockdown of the COVID-19 pandemic. Mental health-related quality-of-life did not differ between in-center hemodialysis and peritoneal dialysis patients.

Gepubliceerd: J Nephrol. 2023;36(7):2037-46.
Impact factor: 3.4 ; Q2

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4. Implementation of Recommendations on the Use of Corticosteroids in Severe COVID-19
Camirand-Lemyre F, Merson L, Tirupakuzhi Vijayaraghavan BK, Burrell AJC, Citarella BW, Domingue MP, Lévesque S, Usuf E, Wils EJ, Ohshimo S, Martin-Loeches I, Sandulescu O, Laake JH, Lamontagne F, ISARIC Clinical Characterisation 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.

Importance: Research diversity and representativeness are paramount in building trust, generating valid biomedical knowledge, and possibly in implementing clinical guidelines.

Objectives: To compare variations over time and across World Health Organization (WHO) geographic regions of corticosteroid use for treatment of severe COVID-19; secondary objectives were to evaluate the association between the timing of publication of the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial (June 2020) and the WHO guidelines for corticosteroids (September 2020) and the temporal trends observed in corticosteroid use by region and to describe the geographic distribution of the recruitment in clinical trials that informed the WHO recommendation.
Design, setting, and participants: This prospective cohort study of 434 851 patients was conducted between January 31, 2020, and September 2, 2022, in 63 countries worldwide. The data were collected under the auspices of the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC)-WHO Clinical Characterisation Protocol for Severe Emerging Infections. Analyses were restricted to patients hospitalized for severe COVID-19 (a subset of the ISARIC data set).
Exposure: Corticosteroid use as reported to the ISARIC-WHO Clinical Characterisation Protocol for Severe Emerging Infections.
Main outcomes and measures: Number and percentage of patients hospitalized with severe COVID-19 who received corticosteroids by time period and by WHO geographic region.
Results: Among 434 851 patients with confirmed severe or critical COVID-19 for whom receipt of corticosteroids could be ascertained (median [IQR] age, 61.0 [48.0-74.0] years; 53.0% male), 174 307 (40.1%) received corticosteroids during the study period. Of the participants in clinical trials that informed the guideline, 91.6% were recruited from the United Kingdom. In all regions, corticosteroid use for severe COVID-19 increased, but this increase corresponded to the timing of the RECOVERY trial (time-interruption coefficient 1.0 [95% CI, 0.9-1.2]) and WHO guideline (time-interruption coefficient 1.9 [95% CI, 1.7-2.0]) publications only in Europe. At the end of the study period, corticosteroid use for treatment of severe COVID-19 was highest in the Americas (5421 of 6095 [88.9%]; 95% CI, 87.7-90.2) and lowest in Africa (31 588 of 185 191 [17.1%]; 95% CI, 16.8-17.3).
Conclusions and relevance: The results of this cohort study showed that implementation of the guidelines for use of corticosteroids in the treatment of severe COVID-19 varied geographically. Uptake of corticosteroid treatment was lower in regions with limited clinical trial involvement. Improving research diversity and representativeness may facilitate timely knowledge uptake and guideline implementation.

Gepubliceerd: JAMA Netw Open. 2023;6(12):e2346502.
Impact factor: 13.8 ; Q1

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5. Neurological manifestations of COVID-19 in adults and children
Cho SM, White N, Premraj L, Battaglini D, Fanning J, Suen J, Bassi GL, Fraser J, Robba C, Griffee M, Singh B, Citarella BW, Merson L, Solomon T, Thomson D, ISARIC Clinical Characterisation 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.

Different neurological manifestations of coronavirus disease 2019 (COVID-19) in adults and children and their impact have not been well characterized. We aimed to determine the prevalence of neurological manifestations and in-hospital complications among hospitalized COVID-19 patients and ascertain differences between adults and children. We conducted a prospective multicentre observational study using the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) cohort across 1507 sites worldwide from 30 January 2020 to 25 May 2021. Analyses of neurological manifestations and neurological complications considered unadjusted prevalence estimates for predefined patient subgroups, and adjusted estimates as a function of patient age and time of hospitalization using generalized linear models. Overall, 161 239 patients (158 267 adults; 2972 children) hospitalized with COVID-19 and assessed for neurological manifestations and complications were included. In adults and children, the most frequent neurological manifestations at admission were fatigue (adults: 37.4%; children: 20.4%), altered

consciousness (20.9%; 6.8%), myalgia (16.9%; 7.6%), dysgeusia (7.4%; 1.9%), anosmia (6.0%; 2.2%) and seizure (1.1%; 5.2%). In adults, the most frequent in-hospital neurological complications were stroke (1.5%), seizure (1%) and CNS infection (0.2%). Each occurred more frequently in intensive care unit (ICU) than in non-ICU patients. In children, seizure was the only neurological complication to occur more frequently in ICU versus non-ICU (7.1% versus 2.3%, P < 0.001). Stroke prevalence increased with increasing age, while CNS infection and seizure steadily decreased with age. There was a dramatic decrease in stroke over time during the pandemic. Hypertension, chronic neurological disease and the use of extracorporeal membrane oxygenation were associated with increased risk of stroke. Altered consciousness was associated with CNS infection, seizure and stroke. All in-hospital neurological complications were associated with increased odds of death. The likelihood of death rose with increasing age, especially after 25 years of age. In conclusion, adults and children have different neurological manifestations and in-hospital complications associated with COVID-19. Stroke risk increased with increasing age, while CNS infection and seizure risk decreased with age.

Gepubliceerd: Brain. 2023;146(4):1648-61.
Impact factor: 14.5 ; Q1

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6. [How long are medical oncology patients in The Netherlands willing to travel for their cancer care?]
de Boer ECS, Versluis MAJ, Vissers PAJ, Slingerland M, Haberkorn BCM, de Ruiter MB, Dingemans IH, van de Poll-Franse LV, Reyners AKL, Wymenga ANM.

Background: The number of people with cancer will increase in the Netherlands. Further concentration and network care is pursued. The aim of this study was to explore how long medical oncology patients are willing to travel for their cancer care.
Method: A flashmob study into patients' willingness to travel for cancer care was conducted in 65 Dutch hospitals. Patients completed a questionnaire about willingness to travel and any experienced issues with traveling.
Results: A total of 4337 medical oncology patients completed the questionnaire. Of the patients, 20% were willing to travel more than 1 hour (one-way) for their current treatment, and more willing to travel for treatment in a hospital more experienced in their specific type of cancer (44% more than 1 hour). Willingness to travel longer was higher among patientsagedv40 years or younger, those with higher education, with better physical functioning and with a rare cancer. Willingness to travel longer was lowest among patients aged 75 or older. Approximately 30% of all patients experienced issues with traveling, especially those with comorbidities or with decreased physical functioning.
Conclusion: In this flashmob study, 15% of patients were willing to travel up to 30 minutes (one-way) and 44% more than 1 hour for treatment and follow-up in a hospital more experienced in their specific type of cancer. Patients aged 75 years or older were less willing to travel longer. Thirty percent of patients experienced issues with travelling. It is important to take this into account in the future organization of cancer care.

Gepubliceerd: Ned Tijdschr Geneeskd. 2023;167.
Impact factor: onbekend

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7. Adjuvant treatment of in-transit melanoma: Narrowing the knowledge gap left by clinical trials
de Meza MM, Blokx WAM, Bonenkamp HJ, Blank CU, Aarts MJB, van den Berkmortel F, Boers-Sonderen MJ, de Groot JWB, Haanen JB, Hospers GAP, Kapiteijn EW, van Not OJ, Piersma D, van Rijn RS, Stevense-Den Boer MA, van der Veldt AAM, Vreugdenhil G, van den Eertwegh AJM, Suijkerbuijk KPM, Wouters M.

Few clinical trials address efficacy of adjuvant systemic treatment in patients with in-transit melanoma (ITM). This study describes adjuvant systemic therapy of ITM patients beyond clinical trials. In this study, we included stage III adjuvant-treated melanoma patients registered in the nationwide Dutch Melanoma Treatment Registry between July 2018 and December 2020. Patients were divided into three groups: nodal disease only, ITM only and ITM and nodal disease. Recurrence patterns, recurrence-free survival (RFS) and overall survival (OS) at 12-months were analyzed. In our study population of 1037 patients, 66.8% had nodal disease only, 16.7% had ITM only and 16.2% had ITM with nodal disease. RFS at 12-months was comparable in the nodal only and ITM only group (72.2% vs70.1%, P = .97) but lower in ITM and nodal disease patients (57.8%; P = .01, P < .01). Locoregional metastases occurred as first recurrence in 38.9% nodal disease only, 71.9% of ITM-only and 44.0% of ITM and nodal disease patients. Distant recurrences occurred in 42.3%, 18.8% and 36.0%, respectively (P = .02). 12-months OS was not significantly different for nodal disease only patients compared with ITM-only (94.4% vs 97.6%, P = .06) but was significantly higher for ITM-only compared with ITM and nodal disease patients (97.6% vs 91.0%, P < .01). In conclusion, we showed that in the adjuvant setting, RFS rates in ITM-only patients are similar to non-ITM, though better than in ITM and nodal disease patients. Adjuvant-treated ITM-only patients less often experience distant recurrences and have a superior OS compared with ITM and nodal disease patients.

Gepubliceerd: Int J Cancer. 2023;153(2):389-98.
Impact factor: 6.4 ; Q1

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8. Adjuvant BRAF-MEK Inhibitors versus Anti PD-1 Therapy in Stage III Melanoma: A Propensity-Matched Outcome Analysis

De Meza MM, Blokx WAM, Bonenkamp JJ, Blank CU, Aarts MJB, van den Berkmortel F, Boers-Sonderen MJ, De Groot JWB, Haanen J, Hospers GAP, Kapiteijn E, Van Not OJ, Piersma D, Van Rijn RS, Stevense-den Boer M, Van der Veldt AAM, Vreugdenhil G, Van den Eertwegh AJM, Suijkerbuijk KPM, Wouters M.

Adjuvant BRAF/MEK- and anti-PD-1 inhibition have significantly improved recurrence-free survival (RFS) compared to placebo in resected stage III BRAF-mutant melanoma. However, data beyond the clinical trial setting are limited. This study describes the toxicity and survival of patients treated with adjuvant BRAF/MEK inhibitors and compares outcomes to adjuvant anti-PD-1. For this study, stage III BRAF V600 mutant cutaneous melanoma patients treated with adjuvant BRAF/MEK-inhibition or anti-PD-1 were identified from the Dutch Melanoma Treatment Registry. BRAF/MEK- and anti-PD-1-treated patients were matched based on propensity scores, and RFS at 12 and 18 months were estimated. Between 1 July 2018 and 31 December 2021, 717 patients were identified. Of these, 114 patients with complete records were treated with BRAF/MEK therapy and 532 with anti-PD-1. Comorbidities (p = 0.04) and geographical region (p < 0.01) were associated with treatment choice. In 45.6% of BRAF/MEK-treated patients, treatment was prematurely discontinued. Grade ≥ 3 toxicity occurred in 11.5% of patients and was the most common cause of early discontinuation (71.1%). At 12 and 18 months, RFS in BRAF/MEK-treated patients was 85% and 70%, compared to 68% and 68% in matched anti-PD-1-treated patients (p = 0.03). In conclusion, comorbidities and geographical region determine the choice of adjuvant treatment in patients with resected stage III BRAF-mutant melanoma. With the currently limited follow-up, BRAF/MEK-treated patients have better RFS at 12 months than matched anti-PD-1-treated patients, but this difference is no longer observed at 18 months. Therefore, longer follow-up data are necessary to estimate long-term effectiveness.

Gepubliceerd: Cancers (Basel). 2023;15(2).
Impact factor: 5.2 ; Q2

9. Health-state utilities in long-term advanced melanoma survivors comparable with the general population

Egeler MD, van de Poll-Franse LV, Tissier R, Rogiers A, Boers-Sonderen MJ, van den Eertwegh AJ, Hospers GA, de Groot JWB, Aarts MJB, Kapiteijn E, Piersma D, Vreugdenhil G, van der Veldt AA, Suijkerbuijk KPM, Neyns B, Janssen KJ, Blank CU, Retèl VP, Boekhout AH.

Background: Checkpoint inhibitors have been shown to substantially improve the survival of patients with advanced melanoma. With this growing group of survivors treated with immunotherapies, assessing their health-state utilities is essential and can be used for the calculation of quality-adjusted life years and for cost-effectiveness analyses. Therefore, we evaluated the health-state utilities in long-term advanced melanoma survivors.
Methods: Health-state utilities were evaluated in a cohort of advanced melanoma survivors 24-36 months (N = 37) and 36-plus months (N = 47) post-ipilimumab monotherapy. In addition, the health-state utilities of the 24-36 months survivor group were assessed longitudinally, and utilities of the combined survival groups (N = 84) were compared with a matched control population (N = 168). The EQ-5D was used to generate health-state utility values, and quality-of-life questionnaires were used to establish correlations and influencing factors of utility scores.
Results: Health-state utility scores were similar between the 24-36 months'- and the 36-plus months' survival group (0.81 vs 0.86; p = .22). In survivors, lower utility scores were associated with symptoms of depression (β = - .82, p = .022) and fatigue burden (β = - .29, p = .007). Utility scores did not significantly change after 24-36 months of survival, and the utilities of survivors were comparable to the matched control population (0.84 vs 0.87; p = .07).
Discussion: Our results show that long-term advanced melanoma survivors treated with ipilimumab monotherapy experience relatively stable and high health-state utility scores.

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Impact factor: 3.5 ; Q2

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10. First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia

Eichhorst B, Niemann CU, Kater AP, Fürstenau M, von Tresckow J, Zhang C, Robrecht S, Gregor M, Juliusson G, Thornton P, Staber PB, Tadmor T, Lindström V, da Cunha-Bang C, Schneider C, Poulsen CB, Illmer T, Schöttker B, Nösslinger T, Janssens A, Christiansen I, Baumann M, Frederiksen H, van der Klift M, Jäger U, Leys MBL, Hoogendoorn M, Lotfi K, Hebart H, Gaska T, Koene H, Enggaard L, Goede J, Regelink JC, Widmer A, Simon F, De Silva N, Fink AM, Bahlo J, Fischer K, Wendtner CM, Kreuzer KA, Ritgen M, Brüggemann M, Tausch E, Levin MD, van Oers M, Geisler C, Stilgenbauer S, Hallek M, HOVON study group: Snijders TJF.

Background: Randomized trials of venetoclax plus anti-CD20 antibodies as first-line treatment in fit patients (i.e., those with a low burden of coexisting conditions) with advanced chronic lymphocytic leukemia (CLL) have been lacking.
Methods: In a phase 3, open-label trial, we randomly assigned, in a 1:1:1:1 ratio, fit patients with CLL who did not have *TP53* aberrations to receive six cycles of chemoimmunotherapy (fludarabine-cyclophosphamide-rituximab or bendamustine-rituximab) or 12 cycles of venetoclax-rituximab, venetoclax-obinutuzumab, or venetoclax-obinutuzumab-ibrutinib. Ibrutinib was discontinued after two consecutive measurements of undetectable minimal residual disease or could be extended. The primary end points were undetectable minimal residual disease (sensitivity, $<10^{-4}$ [i.e., <1 CLL cell in 10,000 leukocytes]) as assessed by flow cytometry in peripheral blood at month 15 and progression-free survival.

Results: A total of 926 patients were assigned to one of the four treatment regimens (229 to chemoimmunotherapy, 237 to venetoclax-rituximab, 229 to venetoclax-obinutuzumab, and 231 to venetoclax-obinutuzumab-ibrutinib). At month 15, the percentage of patients with undetectable minimal residual disease was significantly higher in the venetoclax-obinutuzumab group (86.5%; 97.5% confidence interval [CI], 80.6 to 91.1) and the venetoclax-obinutuzumab-ibrutinib group (92.2%; 97.5% CI, 87.3 to 95.7) than in the chemoimmunotherapy group (52.0%; 97.5% CI, 44.4 to 59.5; P<0.001 for both comparisons), but it was not significantly higher in the venetoclax-rituximab group (57.0%; 97.5% CI, 49.5 to 64.2; P = 0.32). Three-year progression-free survival was 90.5% in the venetoclax-obinutuzumab-ibrutinib group and 75.5% in the chemoimmunotherapy group (hazard ratio for disease progression or death, 0.32; 97.5% CI, 0.19 to 0.54; P<0.001). Progression-free survival at 3 years was also higher with venetoclax-obinutuzumab (87.7%; hazard ratio for disease progression or death, 0.42; 97.5% CI, 0.26 to 0.68; P<0.001), but not with venetoclax-rituximab (80.8%; hazard ratio, 0.79; 97.5% CI, 0.53 to 1.18; P = 0.18). Grade 3 and grade 4 infections were more common with chemoimmunotherapy (18.5%) and venetoclax-obinutuzumab-ibrutinib (21.2%) than with venetoclax-rituximab (10.5%) or venetoclax-obinutuzumab (13.2%).
Conclusions: Venetoclax-obinutuzumab with or without ibrutinib was superior to chemoimmunotherapy as first-line treatment in fit patients with CLL. (Funded by AbbVie and others; GAIA-CLL13 ClinicalTrials.gov number, NCT02950051; EudraCT number, 2015-004936-36.).

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Impact factor: 158.5 ; Q1

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11. Adherence to preventive measures after SARS-CoV-2 vaccination and after awareness of antibody response in kidney transplant recipients in the Netherlands: a nationwide questionnaire study
Frölke SC, Bouwmans P, Messchendorp AL, Vervoort JPM, Abrahams AC, de Vries APJ, Nieuwkerk PT, Hemmelder MH, Gansevoort RT, Hilbrands LB, Reinders MEJ, Sanders JF, Bemelman FJ, Geerlings SE, RECOVAC Collaborators: Brinkman JN.

Background: Kidney transplant recipients (KTRs) were advised to tightly adhere to government recommendations to curb the spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) because of a high risk of morbidity and mortality and decreased immunogenicity after vaccination. The aim of this study was to analyse the change in adherence to preventive measures after vaccination and awareness of antibody response, and to evaluate its effectiveness.
Methods: In this large-scale, national questionnaire study, questionnaires were sent to 3531 KTRs enrolled in the Dutch RECOVAC studies, retrospectively asking for adherence to nine preventive measures on a 5-point Likert scale before and after SARS-CoV-2 vaccination and after awareness of antibody response. Blood samples were collected 28 days after the second vaccination. Antibody response was categorised as non-responder (≤50 BAU/mL), low-responder (>50 ≤ 300 BAU/mL) or high-responder (>300 BAU/mL), and shared with participants as a correlate of protection. Participants of whom demographics on sex and age, blood samples and completed questionnaires were available, were included. Our study took place between February 2021 and January 2022. The primary outcome of adherence before and after vaccination was assessed between August and October 2021 and compared via the Wilcoxon signed rank sum test. Logistic regression analysis was performed to estimate the association between antibody response and non-adherence, and adherence on acquiring SARS-CoV-2 infection. This study is registered at ClinicalTrials.gov (NCT04841785).
Findings: In 2939 KTRs (83%) who completed the first questionnaire on adherence to preventive measures, adherence was higher before than after vaccination (4.56, IQR 4.11-4.78 and 4.22, IQR 3.67-4.67, p < 0.001). Adherence after awareness of antibody response was analysed in 2399 KTRs (82%) of whom also blood samples were available, containing 949 non-responders, 500 low-responders and 950 high-responders. Compared to non-responders, low- and high-responders

reported higher non-adherence. Higher adherence was associated with lower infection rates before and after vaccination (OR 0.67 [0.51-0.91], p = 0.008 and OR 0.48 [0.28-0.86], p = 0.010).
Interpretation: Adherence decreased after SARS-CoV-2 vaccination and in KTRs who were aware of a subsequent antibody response compared with those without. Preventive measures in this vulnerable group seem to be effective, regardless of vaccination status. This study starts a debate on sharing antibody results with the patient and future studies should elucidate whether decreased adherence in antibody responders is justified, also in view of future pandemics.
Funding: The Netherlands Organization for Health Research and Development and the Dutch Kidney Foundation.

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Impact factor: 15.1 ; Q1

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12. Thrombotic and hemorrhagic complications of COVID-19 in adults hospitalized in high-income countries compared with those in adults hospitalized in low- and middle-income countries in an international registry

Griffee MJ, Bozza PT, Reyes LF, Eddington DP, Rosenberger D, Merson L, Citarella BW, Fanning JP, Alexander PMA, Fraser J, Dalton H, Cho SM, ISARIC Clinical Characterisation 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: COVID-19 has been associated with a broad range of thromboembolic, ischemic, and hemorrhagic complications (coagulopathy complications). Most studies have focused on patients with severe disease from high-income countries (HICs).
Objectives: The main aims were to compare the frequency of coagulopathy complications in developing countries (low- and middle-income countries [LMICs]) with those in HICs, delineate the frequency across a range of treatment levels, and determine associations with in-hospital mortality.
Methods: Adult patients enrolled in an observational, multinational registry, the International Severe Acute Respiratory and Emerging Infections COVID-19 study, between January 1, 2020, and September 15, 2021, met inclusion criteria, including admission to a hospital for laboratory-confirmed, acute COVID-19 and data on complications and survival. The advanced-treatment cohort received care, such as admission to the intensive care unit, mechanical ventilation, or inotropes or vasopressors; the basic-treatment cohort did not receive any of these interventions.
Results: The study population included 495,682 patients from 52 countries, with 63% from LMICs and 85% in the basic treatment cohort. The frequency of coagulopathy complications was higher in HICs (0.76%-3.4%) than in LMICs (0.09%-1.22%). Complications were more frequent in the advanced-treatment cohort than in the basic-treatment cohort. Coagulopathy complications were associated with increased in-hospital mortality (odds ratio, 1.58; 95% CI, 1.52-1.64). The increased mortality associated with these complications was higher in LMICs (58.5%) than in HICs (35.4%). After controlling for coagulopathy complications, treatment intensity, and multiple other factors, the mortality was higher among patients in LMICs than among patients in HICs (odds ratio, 1.45; 95% CI, 1.39-1.51).
Conclusion: In a large, international registry of patients hospitalized for COVID-19, coagulopathy complications were more frequent in HICs than in LMICs (developing countries). Increased mortality associated with coagulopathy complications was of a greater magnitude among patients in LMICs. Additional research is needed regarding timely diagnosis of and intervention for coagulation derangements associated with COVID-19, particularly for limited-resource settings.

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Impact factor: 4.6 ; Q2

13. Correction: 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.

[This corrects the article DOI: 10.1371/journal.pmed.1003979.].

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Impact factor: 15.8 ; Q1

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14. Age and sex associate with outcome in older AML and high risk MDS patients treated with 10-day decitabine
Hilberink JR, van Zeventer IA, Chitu DA, Pabst T, Klein SK, Stussi G, Griskevicius L, Valk PJM, Cloos J, van de Loosdrecht AA, Breems D, van Lammeren-Venema D, Boersma R, Jongen-Lavrencic M, Fehr M, Hoogendoorn M, Manz MG, Söhne M, van Marwijk Kooy R, Deeren D, van der Poel MWM, Legdeur MC, Tick L, Chalandon Y, Ammatuna E, Blum S, Löwenberg B, Ossenkoppele GJ, Huls G.

Treatment choice according to the individual conditions remains challenging, particularly in older patients with acute myeloid leukemia (AML) and high risk myelodysplastic syndrome (MDS). The impact of performance status, comorbidities, and physical functioning on survival is not well defined for patients treated with hypomethylating agents. Here we describe the impact of performance status (14% ECOG performance status 2), comorbidity (40% HCT-comorbidity index ≥ 2), and physical functioning (41% short physical performance battery < 9 and 17% ADL index < 6) on overall survival (OS) in 115 older patients (age ≥ 66 years) treated on a clinical trial with a 10-day decitabine schedule. None of the patient-related variables showed a significant association with OS. Multivariable analysis revealed that age > 76 years was significantly associated with reduced OS (HR 1.58; p = 0.043) and female sex was associated with superior OS (HR 0.62; p = 0.06). We further compared the genetic profiles of these subgroups. This revealed comparable mutational profiles in patients younger and older than 76 years, but, interestingly, revealed significantly more prevalent mutated ASXL1, STAG2, and U2AF1 in male compared to female patients. In this cohort of older patients treated with decitabine age and sex, but not comorbidities, physical functioning or cytogenetic risk were associated with overall survival.

Gepubliceerd: Blood Cancer J. 2023;13(1):93.
Impact factor: 12.8 ; Q1

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15. Sex differences in cardiovascular complications and mortality in hospital patients with covid-19: registry based observational study
Hockham C, Linschoten M, Asselbergs FW, Ghossein C, Woodward M, Peters SAE, CAPACITY-COVID Collaborative Consortium: Delsing CE, Meijs MFL.

Objective: To assess whether the risk of cardiovascular complications of covid-19 differ between the sexes and to determine whether any sex differences in risk are reduced in individuals with pre-existing cardiovascular disease.

Design: Registry based observational study.
Setting: 74 hospitals across 13 countries (eight European) participating in CAPACITY-COVID (Cardiac complicAtions in Patients With SARS Corona vIrus 2 regisTrY), from March 2020 to May 2021.
Participants: All adults (aged ≥18 years), predominantly European, admitted to hospital with highly suspected covid-19 disease or covid-19 disease confirmed by positive laboratory test results (n=11 167 patients).
Main outcome measures: Any cardiovascular complication during admission to hospital. Secondary outcomes were in-hospital mortality and individual cardiovascular complications with ≥20 events for each sex. Logistic regression was used to examine sex differences in the risk of cardiovascular outcomes, overall and grouped by pre-existing cardiovascular disease.
Results: Of 11 167 adults (median age 68 years, 40% female participants) included, 3423 (36% of whom were female participants) had pre-existing cardiovascular disease. In both sexes, the most common cardiovascular complications were supraventricular tachycardias (4% of female participants, 6% of male participants), pulmonary embolism (3% and 5%), and heart failure (decompensated or de novo) (2% in both sexes). After adjusting for age, ethnic group, pre-existing cardiovascular disease, and risk factors for cardiovascular disease, female individuals were less likely than male individuals to have a cardiovascular complication (odds ratio 0.72, 95% confidence interval 0.64 to 0.80) or die (0.65, 0.59 to 0.72). Differences between the sexes were not modified by pre-existing cardiovascular disease; for the primary outcome, the female-to-male ratio of the odds ratio in those without, compared with those with, pre-existing cardiovascular disease was 0.84 (0.67 to 1.07).
Conclusions: In patients admitted to hospital for covid-19, female participants were less likely than male participants to have a cardiovascular complication. The differences between the sexes could not be attributed to the lower prevalence of pre-existing cardiovascular disease in female individuals. The reasons for this advantage in female individuals requires further research.

Gepubliceerd: BMJ Med. 2023;2(1):e000245.
Impact factor: onbekend

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16. Immunogenicity of an Additional mRNA-1273 SARS-CoV-2 Vaccination in People With HIV With Hyporesponse After Primary Vaccination

Jongkees MJ, Geers D, Hensley KS, Huisman W, GeurtsvanKessel CH, Bogers S, Gommers L, Papageorgiou G, Jochems SP, den Hollander JG, Schippers EF, Ammerlaan HSM, Bierman WFW, van der Valk M, Berrevoets MAH, Soetekouw R, Langebeek N, Bruns AHW, Leyten EMS, Sigaloff KCE, van Vonderen MGA, Delsing CE, Branger J, Katsikis PD, Mueller YM, de Vries RD, Rijnders BJA, Brinkman K, Rokx C, Roukens AHE.

Background: The COVIH study is a prospective coronavirus disease 2019 (COVID-19) vaccination study in 1154 people with HIV (PWH), of whom 14% showed reduced antibody levels after primary vaccination. We evaluated whether an additional vaccination boosts immune responses in these hyporesponders.
Methods: The primary end point was the increase in antibodies 28 days after additional mRNA-1273 vaccination. Secondary end points included neutralizing antibodies, S-specific T-cell and B-cell responses, and reactogenicity.
Results: Of the 66 participants, 40 previously received 2 doses ChAdOx1-S, 22 received 2 doses BNT162b2, and 4 received a single dose Ad26.COV2.S. The median age was 63 years (interquartile range [IQR], 60-66), 86% were male, and median CD4+ T-cell count was 650/µL (IQR, 423-941). The mean S1-specific antibody level increased from 35 binding antibody units (BAU)/mL (95% confidence interval [CI], 24-46) to 4317 BAU/mL (95% CI, 3275-5360) (P < .0001). Of all participants, 97% showed an adequate response and the 45 antibody-negative participants all seroconverted. A significant increase in the proportion of PWH with ancestral S-specific CD4+ T cells (P = .04) and S-specific B cells (P = .02) was observed.

Conclusions: An additional mRNA-1273 vaccination induced a robust serological response in 97% of PWH with a hyporesponse after primary vaccination. Clinical Trials Registration. EUCTR2021-001054-57-N.

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Impact factor: 6.4 ; Q1

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17. Characteristics and outcomes of an international cohort of 600 000 hospitalized patients with COVID-19
Kartsonaki C, Baillie JK, Barrio NG, Baruch J, Beane A, Blumberg L, Bozza F, Broadley T, Burrell A, Carson G, Citarella BW, Dagens A, Dankwa EA, Donnelly CA, Dunning J, Elotmani L, Escher M, Farshait N, Goffard JC, Gonçalves BP, Hall M, Hashmi M, Sim Lim Heng B, Ho A, Jassat W, Pedrera Jiménez M, Laouenan C, Lissauer S, Martin-Loeches I, Mentré F, Merson L, Morton B, Munblit D, Nekliudov NA, Nichol AD, Singh Oinam BC, Ong D, Panda PK, Petrovic M, Pritchard MG, Ramakrishnan N, Ramos GV, Roger C, Sandulescu O, Semple MG, Sharma P, Sigfrid L, Somers EC, Streinu-Cercel A, Taccone F, Vecham PK, Kumar Tirupakuzhi Vijayaraghavan B, Wei J, Wils EJ, Ci Wong X, Horby P, Rojek A, Olliaro PL, ISARIC Clinical Characterisation 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: We describe demographic features, treatments and clinical outcomes in the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) COVID-19 cohort, one of the world's largest international, standardized data sets concerning hospitalized patients.
Methods: The data set analysed includes COVID-19 patients hospitalized between January 2020 and January 2022 in 52 countries. We investigated how symptoms on admission, co-morbidities, risk factors and treatments varied by age, sex and other characteristics. We used Cox regression models to investigate associations between demographics, symptoms, co-morbidities and other factors with risk of death, admission to an intensive care unit (ICU) and invasive mechanical ventilation (IMV).
Results: Data were available for 689 572 patients with laboratory-confirmed (91.1%) or clinically diagnosed (8.9%) SARS-CoV-2 infection from 52 countries. Age [adjusted hazard ratio per 10 years 1.49 (95% CI 1.48, 1.49)] and male sex [1.23 (1.21, 1.24)] were associated with a higher risk of death. Rates of admission to an ICU and use of IMV increased with age up to age 60 years then dropped. Symptoms, co-morbidities and treatments varied by age and had varied associations with clinical outcomes. The case-fatality ratio varied by country partly due to differences in the clinical characteristics of recruited patients and was on average 21.5%.
Conclusions: Age was the strongest determinant of risk of death, with a ∼30-fold difference between the oldest and youngest groups; each of the co-morbidities included was associated with up to an almost 2-fold increase in risk. Smoking and obesity were also associated with a higher risk of death. The size of our international database and the standardized data collection method make this study a comprehensive international description of COVID-19 clinical features. Our findings may inform strategies that involve prioritization of patients hospitalized with COVID-19 who have a higher risk of death.

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Impact factor: 7.7 ; Q1

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18. Joint models quantify associations between immune cell kinetics and allo-immunological events after allogeneic stem cell transplantation and subsequent donor lymphocyte infusion
Koster EAS, Bonneville EF, Borne P, van Balen P, Marijt EWA, Tjon JML, Snijders TJF, van Lammeren D, Veelken H, Putter H, Falkenburg JHF, Halkes CJM, de Wreede LC.

Alloreactive donor-derived T-cells play a pivotal role in alloimmune responses after allogeneic hematopoietic stem cell transplantation (alloSCT); both in the relapse-preventing Graft-versus-Leukemia (GvL) effect and the potentially lethal complication Graft-versus-Host-Disease (GvHD). The balance between GvL and GvHD can be shifted by removing T-cells via T-cell depletion (TCD) to reduce the risk of GvHD, and by introducing additional donor T-cells (donor lymphocyte infusions [DLI]) to boost the GvL effect. However, the association between T-cell kinetics and the occurrence of allo-immunological events has not been clearly demonstrated yet. Therefore, we investigated the complex associations between the T-cell kinetics and alloimmune responses in a cohort of 166 acute leukemia patients receiving alemtuzumab-based TCD alloSCT. Of these patients, 62 with an anticipated high risk of relapse were scheduled to receive a prophylactic DLI at 3 months after transplant. In this setting, we applied joint modelling which allowed us to better capture the complex interplay between DLI, T-cell kinetics, GvHD and relapse than traditional statistical methods. We demonstrate that DLI can induce detectable T-cell expansion, leading to an increase in total, CD4+ and CD8+ T-cell counts starting at 3 months after alloSCT. CD4+ T-cells showed the strongest association with the development of alloimmune responses: higher CD4 counts increased the risk of GvHD (hazard ratio 2.44, 95% confidence interval 1.45-4.12) and decreased the risk of relapse (hazard ratio 0.65, 95% confidence interval 0.45-0.92). Similar models showed that natural killer cells recovered rapidly after alloSCT and were associated with a lower risk of relapse (HR 0.62, 95%-CI 0.41-0.93). The results of this study advocate the use of joint models to further study immune cell kinetics in different settings.

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Impact factor: 7.3 ; Q1

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19. Competitive Repopulation and Allo-Immunologic Pressure Determine Chimerism Kinetics after T Cell-Depleted Allogeneic Stem Cell Transplantation and Donor Lymphocyte Infusion
Koster EAS, von dem Borne PA, van Balen P, van Egmond EHM, Marijt EWA, Veld SAJ, Jedema I, Snijders TJF, van Lammeren D, Veelken H, Falkenburg JHF, de Wreede LC, Halkes CJM.

After allogeneic stem cell transplantation (alloSCT), patient-derived stem cells that survived the pretransplantation conditioning compete with engrafting donor stem cells for bone marrow (BM) repopulation. In addition, donor-derived alloreactive T cells present in the stem cell product may favor establishment of complete donor-derived hematopoiesis by eliminating patient-derived lymphohematopoietic cells. T cell-depleted alloSCT with sequential transfer of potentially alloreactive T cells by donor lymphocyte infusion (DLI) provides a unique opportunity to selectively study how competitive repopulation and allo-immunologic pressure influence lymphohematopoietic recovery. This study aimed to determine the relative contribution of competitive repopulation and donor-derived anti-recipient alloimmunologic pressure on the establishment of lymphohematopoietic chimerism after alloSCT. In this retrospective cohort study of 281 acute leukemia patients treated according to a protocol combining alemtuzumab-based T cell-depleted alloSCT with prophylactic DLI, we investigated engraftment and quantitative donor chimerism in the BM and immune cell subsets. DLI-induced increase of chimerism and development of graft-versus-host disease (GVHD) were analyzed as complementary indicators for donor-derived anti-recipient alloimmunologic pressure. Profound suppression of patient immune cells by conditioning sufficed for sustained engraftment without necessity for myeloablative conditioning or development of clinically significant GVHD. Although 61% of the patients without any DLI or GVHD showed full donor chimerism (FDC) in the BM at 6 months after alloSCT, only 24% showed FDC in the CD4(+) T cell compartment. In contrast, 75% of the patients who had received DLI and 83% of the patients with clinically significant GVHD had FDC in this compartment. In addition, 72% of the patients with mixed hematopoiesis receiving DLI converted to complete donor-derived hematopoiesis, of whom only 34% developed clinically significant GVHD. Our data show that competitive repopulation can be sufficient to reach complete donor-derived

hematopoiesis, but that some alloimmunologic pressure is needed for the establishment of a completely donor-derived T cell compartment, either by the development of GVHD or by administration of DLI. We illustrate that it is possible to separate the graft-versus-leukemia effect from GVHD, as conversion to durable complete donor-derived hematopoiesis following DLI did not require induction of clinically significant GVHD.

Gepubliceerd: Transplant Cell Ther. 2023;29(4):268.e1-.e10.
Impact factor: 3.2 ; Q2

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20. External validation of the PAGE-B score for HCC risk prediction in people living with HIV/HBV coinfection
Surial B, Ramírez Mena A, Roumet M, Limacher A, Smit C, Leleux O, Mocroft A, van der Valk M, Bonnet F, Peters L, Rockstroh JK, Günthard HF, Berzigotti A, Rauch A, Wandeler G, EuroSIDA collaborators: Kootstra GJ, Delsing CE.

BACKGROUND & AIMS: HBV coinfection is common among people living with HIV (PLWH) and is the most important cause of hepatocellular carcinoma (HCC). While risk prediction tools for HCC have been validated in patients with HBV monoinfection, they have not been evaluated in PLWH. Thus, we performed an external validation of PAGE-B in people with HIV/HBV coinfection. METHODS: We included data on PLWH from four European cohorts who were positive for HBsAg and did not have HCC before starting tenofovir. We estimated the predictive performance of PAGE-B for HCC occurrence over 15 years in patients receiving tenofovir-containing antiretroviral therapy. Model discrimination was assessed after multiple imputation using Cox regression with the prognostic index as a covariate, and by calculating Harrell's c-index. Calibration was assessed by comparing our cumulative incidence with the PAGE-B derivation study using Kaplan-Meier curves. RESULTS: In total, 2,963 individuals with HIV/HBV coinfection on tenofovir-containing antiretroviral therapy were included. PAGE-B was <10 in 26.5%, 10-17 in 57.7%, and ≥18 in 15.7% of patients. Within a median follow-up of 9.6 years, HCC occurred in 68 individuals (2.58/1,000 patient-years, 95% CI 2.03-3.27). The regression slope of the prognostic index for developing HCC within 15 years was 0.93 (95% CI 0.61-1.25), and the pooled c-index was 0.77 (range 0.73-0.80), both indicating good model discrimination. The cumulative incidence of HCC was lower in our study compared to the derivation study. A PAGE-B cut-off of <10 had a negative predictive value of 99.4% for the development of HCC within 5 years. Restricting efforts to individuals with a PAGE-B of ≥10 would spare unnecessary HCC screening in 27% of individuals. CONCLUSIONS: For individuals with HIV/HBV coinfection, PAGE-B is a valid tool to determine the need for HCC screening. IMPACT AND IMPLICATIONS: Chronic HBV infection is the most important cause of hepatocellular carcinoma (HCC) among people living with HIV. Valid risk prediction may enable better targeting of HCC screening efforts to high-risk individuals. We aimed to validate PAGE-B, a risk prediction tool that is based on age, sex, and platelets, in 2,963 individuals with HIV/HBV coinfection who received tenofovir-containing antiretroviral therapy. In the present study, PAGE-B showed good discrimination, adequate calibration, and a cut-off of <10 had a negative predictive value of 99.4% for the development of HCC within 5 years. These results indicate that PAGE-B is a simple and valid risk prediction tool to determine the need for HCC screening among people living with HIV and HBV.

Gepubliceerd: J Hepatol. 2023;78(5):947-57.
Impact factor: 25.7 ; Q1

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21. CT radiomics compared to a clinical model for predicting checkpoint inhibitor treatment outcomes in patients with advanced melanoma

Ter Maat LS, van Duin IAJ, Elias SG, Leiner T, Verhoeff JJC, Arntz E, Troenokarso MF, Blokx WAM, Isgum I, de Wit GA, van den Berkmortel F, Boers-Sonderen MJ, Boomsma MF, van den Eertwegh FJM, de Groot JWB, Piersma D, Vreugdenhil A, Westgeest HM, Kapiteijn E, van Diest PJ, Pluim JPW, de Jong PA, Suijkerbuijk KPM, Veta M.

Introduction: Predicting checkpoint inhibitors treatment outcomes in melanoma is a relevant task, due to the unpredictable and potentially fatal toxicity and high costs for society. However, accurate biomarkers for treatment outcomes are lacking. Radiomics are a technique to quantitatively capture tumour characteristics on readily available computed tomography (CT) imaging. The purpose of this study was to investigate the added value of radiomics for predicting clinical benefit from checkpoint inhibitors in melanoma in a large, multicenter cohort.
Methods: Patients who received first-line anti-PD1±anti-CTLA4 treatment for advanced cutaneous melanoma were retrospectively identified from nine participating hospitals. For every patient, up to five representative lesions were segmented on baseline CT, and radiomics features were extracted. A machine learning pipeline was trained on the radiomics features to predict clinical benefit, defined as stable disease for more than 6 months or response per RECIST 1.1 criteria. This approach was evaluated using a leave-one-centre-out cross validation and compared to a model based on previously discovered clinical predictors. Lastly, a combination model was built on the radiomics and clinical model.
Results: A total of 620 patients were included, of which 59.2% experienced clinical benefit. The radiomics model achieved an area under the receiver operator characteristic curve (AUROC) of 0.607 [95% CI, 0.562-0.652], lower than that of the clinical model (AUROC=0.646 [95% CI, 0.600-0.692]). The combination model yielded no improvement over the clinical model in terms of discrimination (AUROC=0.636 [95% CI, 0.592-0.680]) or calibration. The output of the radiomics model was significantly correlated with three out of five input variables of the clinical model ($p < 0.001$).
Discussion: The radiomics model achieved a moderate predictive value of clinical benefit, which was statistically significant. However, a radiomics approach was unable to add value to a simpler clinical model, most likely due to the overlap in predictive information learned by both models. Future research should focus on the application of deep learning, spectral CT-derived radiomics, and a multimodal approach for accurately predicting benefit to checkpoint inhibitor treatment in advanced melanoma.

Gepubliceerd: Eur J Cancer. 2023;185:167-77.
Impact factor: 8.4 ; Q1

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22. Population mortality in advanced melanoma patients with and without response and progression; data from the Dutch Melanoma Treatment Registry
van Breeschoten J, van den Eertwegh AJM, Hilarius DL, 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, Manevski D, Suijkerbuijk KPM, Wouters M, de Wreede LC.

Introduction: When analysing patient survival, one is often interested in cause of death. Little is known about the presence of population mortality in advanced melanoma patients. The aim of this study was to assess population mortality after different response states in advanced melanoma patients in the Netherlands, and analyse the contribution of disease and population mortality for different age groups.
Methods: We selected patients diagnosed between 2013 and 2019 with unresectable IIIC or stage IV melanoma, registered in the Dutch Melanoma Treatment Registry. A multi-state model with response states integrating population mortality was fitted. One-year landmark analyses were performed to assess outcomes after each response state.

Results: Overall, 5119 patients were selected. Five-year probabilities of melanoma-related mortality in patients alive in complete response at one year after diagnosis increased with age, and was 17.2% (95% confidence interval: 13.0-21.4) for patients aged <65 years and 28.7% (95% confidence interval: 24.3-33.1) in patients aged ≥80 years. Population mortality only played a large role for older patients (75 years and above) alive at 1 year after diagnosis with a partial or complete response.
Conclusion: Even though survival outcomes of advanced melanoma patients have improved over the last decade, the vast majority of patients still die due to melanoma-related mortality.

Gepubliceerd: Eur J Cancer. 2023;182:132-43.
Impact factor: 8.4 ; Q1

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23. Failure to validate existing clinical prediction scale for response to PD-1 monotherapy in advanced melanoma in national cohort study
van der Kooij MK, Joosse A, Suijkerbuijk KPM, Aarts MJB, van den Berkmortel F, Blank CU, Boers-Sonderen MJ, van den Eertwegh AJM, de Groot JWB, Haanen J, Hospers GAP, Piersma D, van Rijn RS, van der Veldt AAM, Vreugdenhil G, Westgeest HM, Wouters M, Dekkers OM, Kapiteijn E.

Gepubliceerd: Br J Cancer. 2023;128(5):707-10.
Impact factor: 8.8 ; Q1

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24. Feasibility, safety, and efficacy of early prophylactic donor lymphocyte infusion after T cell-depleted allogeneic stem cell transplantation in acute leukemia patients
van der Zouwen B, Koster EAS, von dem Borne PA, Oosten LEM, Roza-Scholten MWI, Snijders TJF, van Lammeren D, van Balen P, Marijt WAF, Veelken H, Falkenburg JHF, de Wreede LC, Halkes CJM.

Prophylactic donor lymphocyte infusion (DLI) starting at 6 months after T cell-depleted allogeneic stem cell transplantation (TCD-alloSCT) can introduce a graft-versus-leukemia (GvL) effects with low risk of severe graft-versus-host-disease (GvHD). We established a policy to apply low-dose early DLI at 3 months after alloSCT to prevent early relapse. This study analyzes this strategy retrospectively. Of 220 consecutive acute leukemia patients undergoing TCD-alloSCT, 83 were prospectively classified to have a high relapse risk and 43 were scheduled for early DLI. 95% of these patients received freshly harvested DLI within 2 weeks of the planned date. In patients transplanted with reduced intensity conditioning and an unrelated donor, we found an increased cumulative incidence of GvHD between 3 and 6 months after TCD-alloSCT for patients receiving DLI at 3 months compared to patients who did not receive this DLI (0.42 (95%Confidence Interval (95% CI): 0.14-0.70) vs 0). Treatment success was defined as being alive without relapse or need for systemic immunosuppressive GvHD treatment. The five-year treatment success in patients with acute lymphatic leukemia was comparable between high- and non-high-risk disease (0.55 (95% CI: 0.42-0.74) and 0.59 (95% CI: 0.42-0.84)). It remained lower in high-risk acute myeloid leukemia (AML) (0.29 (95% CI: 0.18-0.46)) than in non-high-risk AML (0.47 (95% CI: 0.42-0.84)) due to an increased relapse rate despite early DLI.

Gepubliceerd: Ann Hematol. 2023;102(5):1203-13.
Impact factor: 3.5 ; Q2

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25. Time interval from primary melanoma to first distant recurrence in relation to patient outcomes in advanced melanoma
van Duin IAJ, Elias SG, van den Eertwegh AJM, de Groot JWB, Blokx WAM, van Diest PJ, Leiner T, Verhoeff JJC, Verheijden RJ, van Not OJ, Aarts MJB, van den Berkmortel F, Blank CU, Haanen J,

Hospers GAP, Kamphuis AM, Piersma D, van Rijn RS, van der Veldt AAM, Vreugdenhil G, Wouters M, Stevense-den Boer MAM, Boers-Sonderen MJ, Kapiteijn E, Suijkerbuijk KPM.

Since the introduction of BRAF(/MEK) inhibition and immune checkpoint inhibition (ICI), the prognosis of advanced melanoma has greatly improved. Melanoma is known for its remarkably long time to first distant recurrence (TFDR), which can be decades in some patients and is partly attributed to immune-surveillance. We investigated the relationship between TFDR and patient outcomes after systemic treatment for advanced melanoma. We selected patients undergoing first-line systemic therapy for advanced melanoma from the nationwide Dutch Melanoma Treatment Registry. The association between TFDR and progression-free survival (PFS) and overall survival (OS) was assessed by Cox proportional hazard regression models. The TFDR was modeled categorically, linearly, and flexibly using restricted cubic splines. Patients received anti-PD-1-based treatment (n = 1844) or BRAF(/MEK) inhibition (n = 1618). For ICI-treated patients with a TFDR <2 years, median OS was 25.0 months, compared to 37.3 months for a TFDR >5 years (P = .014). Patients treated with BRAF(/MEK) inhibition with a longer TFDR also had a significantly longer median OS (8.6 months for TFDR <2 years compared to 11.1 months for >5 years, P = .004). The hazard of dying rapidly decreased with increasing TFDR until approximately 5 years (HR 0.87), after which the hazard of dying further decreased with increasing TFDR, but less strongly (HR 0.82 for a TFDR of 10 years and HR 0.79 for a TFDR of 15 years). Results were similar when stratifying for type of treatment. Advanced melanoma patients with longer TFDR have a prolonged PFS and OS, irrespective of being treated with first-line ICI or targeted therapy.

Gepubliceerd: Int J Cancer. 2023;152(12):2493-502.
Impact factor: 6.4 ; Q1

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26. Response to checkpoint inhibition and targeted therapy in melanoma patients with concurrent haematological malignancies
Van Not OJ, van den Eertwegh AJM, Haanen JB, van Rijn RS, Aarts MJB, van den Berkmortel F, Blank CU, Boers-Sonderen MJ, van Eijs MJM, de Groot JB, Hospers GAP, Kapiteijn E, de Meza M, Piersma D, Stevense-den Boer M, van der Veldt AAM, Vreugdenhil G, Wouters M, Suijkerbuijk KPM, Blokx WAM.

Background: Patients diagnosed with haematologic malignancies (HMs) have a higher risk of developing subsequent solid tumours, such as melanoma. Patients with HM were mostly excluded from clinical trials but potentially derive less benefit from immune checkpoint inhibitors (ICIs) due to disease- or treatment-related T- or B-cell dysfunction.
Methods: All advanced melanoma patients treated with anti-PD-1-based treatment or targeted therapy between 2015 and 2021 were included from the prospective nationwide Dutch Melanoma Treatment Registry. Progression-free survival (PFS) and melanoma-specific survival (MSS) were analysed for patients with HM (HM+) and without HM (HM-). A cox model was used to account for confounders associated with PFS and MSS.
Results: In total, 4638 advanced melanoma patients received first-line anti-PD-1 monotherapy (n = 1763), ipilimumab-nivolumab (n = 800), or BRAF(/MEK) inhibitors (n = 2075). Concurrent HMs were present for 46 anti-PD1-treated patients, 11 ipilimumab-nivolumab-treated patients and 43 BRAF(/MEK)-inhibitor-treated patients. In anti-PD-1-treated patients, the median PFS was 2.8 months for HM+ and 9.9 months for HM- (p = 0.01). MSS was 41.2 months for HM+ and 58.1 months for HM- (p = 0.00086). In multivariable analysis, the presence of an HM was significantly associated with higher risk of melanoma progression (HR_{adj} 1.62; 95% confidence interval [95% CI] 1.15-2.29; p = 0.006) and melanoma-related death (HR_{adj} 1.74; 95% CI 1.09-2.78; p = 0.020). Median PFS and MSS for first-line BRAF(/MEK-) inhibitor-treated HM+ and HM- patients were not significantly different.

Conclusions: Patients with HM and advanced melanoma show significantly worse melanoma-related outcomes when treated with ICI, but not targeted therapy, compared to patients without HM. Clinicians should be aware of potentially altered effectiveness of ICI in patients with active HM.

Gepubliceerd: Eur J Cancer. 2023;186:27-37.
Impact factor: 8.4 ; Q1

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27. A Survival Tree of Advanced Melanoma Patients with Brain Metastases Treated with Immune Checkpoint Inhibitors
van Not OJ, Wind TT, Ismail RK, Bhattacharya A, Jalving M, Blank CU, Aarts MJB, van den Berkmortel F, Boers-Sonderen MJ, van den Eertwegh AJM, de Groot JWB, Haanen JB, Kapiteijn E, Bloem M, Piersma D, van Rijn RS, Stevense-den Boer M, van der Veldt AAM, Vreugdenhil G, Wouters M, Blokx WAM, Suijkerbuijk KPM, Fehrmann RSN, Hospers GAP.

The efficacy of immune checkpoint inhibitors (ICIs) in patients with advanced melanoma that develop brain metastases (BM) remains unpredictable. In this study, we aimed to identify prognostic factors in patients with melanoma BM who are treated with ICIs. Data from advanced melanoma patients with BM treated with ICIs in any line between 2013 and 2020 were obtained from the Dutch Melanoma Treatment Registry. Patients were included from the time of the treatment of BM with ICIs. Survival tree analysis was performed with clinicopathological parameters as potential classifiers and overall survival (OS) as the response variable. In total, 1278 patients were included. Most patients were treated with ipilimumab-nivolumab combination therapy (45%). The survival tree analysis resulted in 31 subgroups. The median OS ranged from 2.7 months to 35.7 months. The strongest clinical parameter associated with survival in advanced melanoma patients with BM was the serum lactate dehydrogenase (LDH) level. Patients with elevated LDH levels and symptomatic BM had the worst prognosis. The clinicopathological classifiers identified in this study can contribute to optimizing clinical studies and can aid doctors in giving an indication of the patients' survival based on their baseline and disease characteristics.

Gepubliceerd: Cancers (Basel). 2023;15(11).
Impact factor: 5.2 ; Q2

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28. Real-world Outcomes of Ipilimumab Plus Nivolumab Combination Therapy in a Nation-wide Cohort of Advanced Melanoma Patients in the Netherlands
van Zeijl MCT, van Breeschoten J, de Wreede LC, Wouters M, Hilarius DL, 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, Haanen J, van den Eertwegh AJM.

In phase III trials, ipilimumab plus nivolumab combination therapy is highly efficacious for advanced melanoma, despite many treatment-related grades 3-4 adverse events. Here, we report real-world safety and survival outcomes of ipilimumab plus nivolumab for advanced melanoma. Patients with advanced melanoma who received first-line ipilimumab plus nivolumab between January 1, 2015 and June 30, 2021 were selected from the Dutch Melanoma Treatment Registry. We evaluated response status at 3, 6, 12, 18, and 24 months. OS and PFS were estimated with the Kaplan-Meier method. Separate analyses were performed for patients with or without brain metastases and for patients who met the inclusion criteria of the Checkmate-067 trial. In total, 709 patients received first-line ipilimumab plus nivolumab. Three hundred sixty (50.7%) patients experienced grade 3-4 adverse events, with 211 of the (58.6%) patients requiring hospital admission. The median treatment duration

was 42 days (IQR = 31-139). At 24 months, disease control was achieved in 37% of patients. Median PFS since the start of treatment was 6.6 months (95% CI: 5.3-8.7), and median OS was 28.7 months (95% CI: 20.7-42.2). CheckMate-067 trial-like patients had a 4-year OS of 50% (95% CI: 43-59). Among patients with no asymptomatic or symptomatic brain metastases, the 4-year OS probabilities were 48% (95% CI: 41-55), 45% (95% CI: 35-57), and 32% (95% CI: 23-46). Ipilimumab plus nivolumab can achieve long-term survival in advanced melanoma patients in a real-world setting, including patients not represented in the CheckMate-067 trial. However, the proportion of patients with disease control in the real world is lower compared with clinical trials.

Gepubliceerd: J Immunother. 2023;46(5):197-204.
Impact factor: 3.9 ; Q3

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29. Association of Country Income Level With the Characteristics and Outcomes of Critically Ill Patients Hospitalized With Acute Kidney Injury and COVID-19
Wainstein M, Spyrison N, Dai D, Ghadimi M, Chávez-Iñiguez JS, Rizo-Topete L, Citarella BW, Merson L, Pole JD, Claure-Del Granado R, Johnson DW, Shrapnel S, ISARIC Clinical Characterisation 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.

Introduction: Acute kidney injury (AKI) has been identified as one of the most common and significant problems in hospitalized patients with COVID-19. However, studies examining the relationship between COVID-19 and AKI in low- and low-middle income countries (LLMIC) are lacking. Given that AKI is known to carry a higher mortality rate in these countries, it is important to understand differences in this population.
Methods: This prospective, observational study examines the AKI incidence and characteristics of 32,210 patients with COVID-19 from 49 countries across all income levels who were admitted to an intensive care unit during their hospital stay.
Results: Among patients with COVID-19 admitted to the intensive care unit, AKI incidence was highest in patients in LLMIC, followed by patients in upper-middle income countries (UMIC) and high-income countries (HIC) (53%, 38%, and 30%, respectively), whereas dialysis rates were lowest among patients with AKI from LLMIC and highest among those from HIC (27% vs. 45%). Patients with AKI in LLMIC had the largest proportion of community-acquired AKI (CA-AKI) and highest rate of in-hospital death (79% vs. 54% in HIC and 66% in UMIC). The association between AKI, being from LLMIC and in-hospital death persisted even after adjusting for disease severity.
Conclusions: AKI is a particularly devastating complication of COVID-19 among patients from poorer nations where the gaps in accessibility and quality of healthcare delivery have a major impact on patient outcomes.

Gepubliceerd: Kidney Int Rep. 2023;8(8):1514-30.
Impact factor: 6.0 ; Q1

Totale impact factor: 370.5
Gemiddelde impact factor: 12.8

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 1
Totale impact factor: NVT (onbekend)
Gemiddelde impact factor: NVT (onbekend)

Kindergeneeskunde

1. Group A streptococcal disease in paediatric inpatients: a European perspective
Boeddha NP, Atkins L, de Groot R, Driessen G, Hazelzet J, Zenz W, Carrol ED, Anderson ST, Martinon-Torres F, Agyeman PKA, Galassini R, Herberg J, Levin M, Schlapbach LJ, Emonts M, EUCLIDS consortium: Thio BJ.

Group A streptococcal (GAS) disease shows increasing incidence worldwide. We characterised children admitted with GAS infection to European hospitals and studied risk factors for severity and disability. This is a prospective, multicentre, cohort study (embedded in EUCLIDS and the Swiss Pediatric Sepsis Study) including 320 children, aged 1 month to 18 years, admitted with GAS infection to 41 hospitals in 6 European countries from 2012 to 2016. Demographic, clinical, microbiological and outcome data were collected. A total of 195 (61%) patients had sepsis. Two hundred thirty-six (74%) patients had GAS detected from a normally sterile site. The most common infection sites were the lower respiratory tract (LRTI) (22%), skin and soft tissue (SSTI) (23%) and bone and joint (19%). Compared to patients not admitted to PICU, patients admitted to PICU more commonly had LRTI (39 vs 8%), infection without a focus (22 vs 8%) and intracranial infection (9 vs 3%); less commonly had SSTI and bone and joint infections ($p < 0.001$); and were younger (median 40 (IQR 21-83) vs 56 (IQR 36-85) months, $p = 0.01$). Six PICU patients (2%) died. Sequelae at discharge from hospital were largely limited to patients admitted to PICU (29 vs 3%, $p < 0.001$; 12% overall) and included neurodisability, amputation, skin grafts, hearing loss and need for surgery. More patients were recruited in winter and spring ($p < 0.001$). CONCLUSION: In an era of observed marked reduction in vaccine-preventable infections, GAS infection requiring hospital admission is still associated with significant severe disease in younger children, and short- and long-term morbidity. Further advances are required in the prevention and early recognition of GAS disease. WHAT IS KNOWN: • Despite temporal and geographical variability, there is an increase of incidence of infection with group A streptococci. However, data on the epidemiology of group A streptococcal infections in European children is limited. WHAT IS NEW: • In a large, prospective cohort of children with community-acquired bacterial infection requiring hospitalisation in Europe, GAS was the most frequent pathogen, with 12% disability at discharge, and 2% mortality in patients with GAS infection. • In children with GAS sepsis, IVIG was used in only 4.6% of patients and clindamycin in 29% of patients.

Gepubliceerd: Eur J Pediatr. 2023;182(2):697-706.
Impact factor: 3.6 ; Q1

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2. EUFOREA pocket guide on the diagnosis and management of asthma: An educational and practical tool for general practitioners, non-respiratory physicians, paramedics and patients
Diamant Z, Jesenak M, Hanania NA, Heaney LG, Djukanovic R, Ryan D, Quirce S, Backer V, Gaga M, Pavord I, Antolín-Amérigo D, Assaf S, Bakakos P, Bobcakova A, Busse W, Kappen J, Loukides S, van Maaren M, Panzner P, Pite H, Spanevello A, Stenberg H, Striz I, Thio B, Vasakova MK, Conti D, Fokkens W, Lau S, Scadding GK, Van Staeyen E, Hellings PW, Bjermer L.

Gepubliceerd: Respir Med. 2023;218:107361.
Impact factor: 4.3 ; Q2

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3. Improved clinical outcomes with early anti-tumour necrosis factor alpha therapy in children with newly diagnosed Crohn's disease: real world data from the international prospective PIBD-SETQuality inception cohort study

Klomberg RCW, van der Wal HC, Aardoom MA, Kemos P, Rizopoulos D, Ruemmele FM, Charrout M, Escher JC, Croft NM, de Ridder L, Milovanovich ID, Ashton JJ, Henderson P, Ledder O, de Meij TGJ, Hansen R, Hummel TZ, Arai K, Rodrigues A, Cameron F, Koletzko S, Muhammed R, Nedelkopoulou N.

Background and aims: Treatment guidelines for paediatric Crohn's disease [CD] suggest early use of anti-tumour necrosis factor alpha [anti-TNFα] in high-risk individuals. The aim is to evaluate the effect of early anti-TNF in a real-world cohort.
Methods: Children with newly diagnosed CD were prospectively recruited at 28 participating sites of the international observational PIBD-SETQuality study. Outcomes were compared at 3 months, 1 and 2 years between patients receiving early anti-TNF [<90 days after diagnosis] and those not receiving early anti-TNF. Outcomes included sustained steroid-free remission [SSFR] without treatment intensification [specified as SSFR*] and sustained steroid-free mild/inactive disease without treatment intensification [specified as SSFMI*]. Penalised logistic regression model-based standardisation was applied to estimate the relative risks [RR] of early therapy on outcomes. RRs were estimated for high-risk and low-risk patients, based on presence of predictors of poor outcome [POPOs] and disease activity at diagnosis.
Results: In total, 331 children (median age 13.9 years [IQR 12.2-15.3]) were enrolled, with 135 [41%] receiving early anti-TNF. At 1 year, patients on early anti-TNF had higher rates of SSFR* [30% vs 14%, p <0.001] and SSFMI* [69% vs 33%, p <0.001], with RRs of 2.95 [95% CI 1.63-5.36] and 4.67 [95% CI 2.46-8.87], respectively. At 1 year, the RRs for SSFMI* were higher, and statistically significant in high-risk patients, i.e. those with moderate/severe disease compared with mild/inactive disease at diagnosis (5.50 [95% CI 2.51-12.05] vs 2.91 [95% CI 0.92-9.11]), and those with any POPO compared with no POPO (5.05 [95% CI 2.45-10.43] vs 3.41 [95% CI 0.54-21.7]).
Conclusion: In this cohort of children with newly-diagnosed CD, early anti-TNF demonstrated superior effectiveness in high-risk patients.

Gepubliceerd: J Crohns Colitis. 2023.
Impact factor: 8.0 ; Q1

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4. Conservative Treatment of Parapneumonic Effusion in Children: Experience From a 10-Year Consecutive Case Series
Lohuis SJ, de Groot E, Kamps AWA, Ottink MD, de Vries TW, Bekhof J.

Background: In children with parapneumonic effusion (PPE), it remains unclear when conservative treatment with antibiotics suffixes or when pleural drainage is needed. In this study we evaluate clinical features and outcomes of children with PPE.
Methods: A retrospective, multicentre cohort study at 4 Dutch pediatric departments was performed, including patients 1-18 years treated for PPE between January 2010 and June 2020.
Results: One hundred thirty-six patients were included (mean age 8.3 years, SD 4.8). 117 patients (86%) were treated conservatively and 19 (14%) underwent pleural drainage. Patients undergoing pleural drainage had mediastinal shift more frequently compared with conservatively treated patients (58 vs. 3%, difference 55%; 95% CI: 32%-77%). The same accounted for pleural septations/pockets (58 vs. 11%, difference 47%; 95% CI: 24%-70%), pleural thickening (47 vs. 4%, difference 43%; 95% CI: 20%-66%) and effusion size (median 5.9 vs. 2.7 cm; P = 0.032). Conservative management was successful in 27% of patients (4 of 15) with mediastinal shift, 54% of patients (13 of 24) with septations/pockets, 36% of patients (5 of 14) with pleural thickening, and 9% of patients (3 of 32) with effusions >3 cm, all radiological signs generally warranting pleural drainage. In patients treated conservatively, median duration of hospitalization was 5 days (IQR 4-112) compared with 19 days (IQR 15-24) in the drainage group (P < 0.001), without significant difference in readmission rate (11 vs. 4%, difference 6%; 95% CI: -8%-21%).

Conclusion: This study suggests that the greater amount of children with PPE could be treated conservatively with antibiotics only, especially in absence of mediastinal shift, pleural septations/pockets, pleural thickening or extensive effusions.

Gepubliceerd: Pediatr Infect Dis J. 2023;42(3):180-3.
Impact factor: 3.6 ; Q3

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5. Daily intranasal palivizumab to prevent respiratory syncytial virus infection in healthy preterm infants: a phase 1/2b randomized placebo-controlled trial
Mazur NI, Löwensteyn YN, Terstappen J, Leusen J, Schobben F, Cianci D, van de Ven PM, Nierkens S, Bont LJ, Narsyn Study Group: van Rooij LGM.

Background: Mucosal administration of monoclonal antibodies (mAbs) against respiratory pathogens is a promising alternative for systemic administration because lower doses are required for protection. Clinical development of mucosal mAbs is a highly active field yet clinical proof-of-concept is lacking.
Methods: In this investigator-initiated, double-blind, randomized placebo-controlled trial, we evaluated intranasal palivizumab for the prevention of RSV infection in preterm infants (Dutch Trial Register NTR7378 and NTR7403). We randomized infants 1:1 to receive intranasal palivizumab (1 mg/mL) or placebo once daily during the RSV season. Any RSV infection was the primary outcome and RSV hospitalization was the key secondary outcome. The primary outcome was analyzed with a mixed effect logistic regression on the modified intention-to-treat population.
Findings: We recruited 268 infants between Jan 14, 2019 and Jan 28, 2021, after which the trial was stopped for futility following the planned interim analysis. Adverse events were similar in both groups (22/134 (16.4%) palivizumab arm versus 26/134 (19.4%) placebo arm). There were 6 dropouts and 168 infants were excluded from the efficacy analyses due to absent RSV circulation during the SARS-CoV-2 pandemic. Any RSV infection was similar in infants in both groups (18/47 (38.3%) palivizumab arm versus 11/47 (23.4%) placebo arm; aOR 2.2, 95% CI 0.7-6.5).
Interpretation: Daily intranasal palivizumab did not prevent RSV infection in late preterm infants. Our findings have important implications for the clinical development of mucosal mAbs, namely the necessity of timely interim analyses and further research to understand mucosal antibody half-life.
Funding: Funded by the Department of Pediatrics, University Medical Centre Utrecht, the Netherlands.

Gepubliceerd: EClinicalMedicine. 2023;66:102324.
Impact factor: 15.1 ; Q1

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6. eHealth Technologies for Monitoring Pediatric Asthma at Home: Scoping Review
van der Kamp MR, Hengeveld VS, Brusse-Keizer MGJ, Thio BJ, Tabak M.

Background: eHealth monitoring technologies offer opportunities to more objectively assess symptoms when they appear in daily life. Asthma is the most common chronic disease in childhood with an episodic course, requiring close follow-up of pediatric asthma control to identify disease deterioration, prevent exacerbations, and enhance quality of life. eHealth technologies in pediatric asthma care show promising results regarding feasibility, acceptability, and asthma-related health outcomes. However, broad systematic evaluations of eHealth technologies in pediatric asthma are lacking.

Objective: The objective of this scoping review was to identify the types and applications of eHealth technologies for monitoring and treatment in pediatric asthma and explore which monitoring domains show the most relevance or potential for future research.
Methods: A scoping review was conducted using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. A systematic and comprehensive search was performed on English papers that investigated the development, validation, or application of eHealth technologies for home monitoring or treatment of pediatric asthma in the following databases: PubMed, Cochrane Library, IEEE, Scopus, CINAHL, PsycINFO, and ACM Digital Library. Two authors independently assessed eligibility and extracted data. Data were presented by a descriptive analysis of characteristics and a narrative report for each eHealth domain.
Results: The review included 370 manuscripts. The following 10 monitoring domains were identified: air quality, airway inflammation markers, lung function, physical activity, sleep, audiovisual, other physiological measurements, questionnaires, medication monitoring, and digital environment (ie, digital platforms, applications, websites, and software tools to monitor or support monitoring). Rising numbers of studies were seen, and the numbers accelerated in the last few years throughout most domains, especially medication monitoring and digital environment. Limited studies (35/370, 9.5%) of multiparameter monitoring strategies, using three or more domains, were found. The number of monitoring validation studies remained stable, while development and intervention studies increased. Intervention outcomes seemed to indicate the noninferiority and potential superiority of eHealth monitoring in pediatric asthma.
Conclusions: This systematic scoping review provides a unique overview of eHealth pediatric asthma monitoring studies, and it revealed that eHealth research takes place throughout different monitoring domains using different approaches. The outcomes of the review showed the potency for efficacy of most monitoring domains (especially the domains of medication monitoring, lung function, and digital environment). Future studies could focus on modifying potentially relevant hospital-based diagnostics for the home setting to investigate potential beneficial effects and focus on combining home-monitoring domains to facilitate multiparameter decision-making and personalized clinical decision support.

Gepubliceerd: J Med Internet Res. 2023;25:e45896.
Impact factor: 7.4 ; Q1

Totale impact factor: 42.0
Gemiddelde impact factor: 7.0

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 1
Totale impact factor: 7.4
Gemiddelde impact factor: 7.4

Klinische chemie

1. The first trimester plasma copper-zinc ratio is independently related to pregnancy-specific psychological distress symptoms throughout pregnancy
Hulsbosch LP, Boekhorst M, Gigase FAJ, Broeren MAC, Krabbe JG, Maret W, Pop VJM.

Objectives: High plasma copper (Cu) and low zinc (Zn) levels have been associated with depression. However, most studies used low sample sizes and a cross-sectional design, and perinatal data are scarce. We investigated the possible association between pregnancy-specific psychological distress and the plasma CuZn ratio using a prospective design.
Methods: Pregnancy-specific distress symptoms were assessed at each trimester by means of the Tilburg Pregnancy Distress Scale, negative affect subscale, in 2036 pregnant women. Cu and Zn were assessed at 12 wk of gestation in plasma samples by inductively coupled plasma mass spectrometry. Growth mixture modeling determined trajectories of women's pregnancy-specific negative affect (P-NA) symptoms, which were entered in a multiple logistic regression analysis as dependent variable and the CuZn ratio as independent variable.
Results: Two P-NA symptom classes were found: 1) persistently low (n = 1820) and 2) persistently high (n = 216). A higher CuZn ratio was independently associated with persistently high P-NA symptom scores (odds ratio = 1.52; 95% confidence interval, 1.13-2.04) after adjustment for confounders. A sensitivity analysis was performed excluding all women with high P-NA scores at 12 wk of gestation (>1 SD above the mean P-NA score). In the 1719 remaining women, a higher CuZn ratio significantly predicted the development of increasing P-NA symptom scores after adjustment for confounders (odds ratio = 1.40; 95% confidence interval, 1.04-1.95).
Conclusions: A higher CuZn plasma ratio is an independent determinant of developing pregnancy-specific distress symptoms throughout pregnancy, suggesting that micronutrients could be used as novel biomarkers for psychological distress research of perinatal mood disorders.

Gepubliceerd: Nutrition. 2023;109:111938.
Impact factor: 4.4 ; Q2

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2. Analytical assay validation for acute myeloid leukemia measurable residual disease assessment by multiparametric flow cytometry
Tettero JM, Dakappagari N, Heidinga ME, Oussoren-Brockhoff Y, Hanekamp D, Pahuja A, Burns K, Kaur P, Alfonso Z, van der Velden VHJ, Te Marvelde JG, Hobo W, Slomp J, Bachas C, Kelder A, Nguyen K, Cloos J.

Background: Measurable residual disease (MRD) assessed by multiparametric flow cytometry (MFC) has gained importance in clinical decision-making for acute myeloid leukemia (AML) patients. However, complying with the recent In Vitro Diagnostic Regulations (IVDR) in Europe and Food and Drug Administration (FDA) guidance in the United States requires rigorous validation prior to their use in investigational clinical trials and diagnostics. Validating AML MRD-MFC assays poses challenges due to the unique underlying disease biology and paucity of patient specimens. In this study, we describe an experimental framework for validation that meets regulatory expectations.
Methods: Our validation efforts focused on evaluating assay accuracy, analytical specificity, analytical and functional sensitivity (limit of blank (LoB), detection (LLoD) and quantitation (LLoQ)), precision, linearity, sample/reagent stability and establishing the assay background frequencies.
Results: Correlation between different MFC methods was highly significant (r = 0.99 for %blasts and r = 0.93 for %LAIPs). The analysis of LAIP specificity accurately discriminated from negative control cells. The assay demonstrated a LoB of 0.03, LLoD of 0.04, and LLoQ of 0.1%. Precision experiments yielded highly reproducible results (Coefficient of Variation <20%). Stability experiments

demonstrated reliable measurement of samples up to 96 h from collection. Furthermore, the reference range of LAIP frequencies in non-AML patients was below 0.1%, ranging from 0.0% to 0.04%.
Conclusion: In this manuscript, we present the validation of an AML MFC-MRD assay using BM/PB patient specimens, adhering to best practices. Our approach is expected to assist other laboratories in expediting their validation activities to fulfill recent health authority guidelines.

Gepubliceerd: Cytometry B Clin Cytom. 2023;104(6):426-39.
Impact factor: 3.4 ; Q2

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3. Analytical interference of intravascular contrast agents with clinical laboratory tests: a joint guideline by the ESUR Contrast Media Safety Committee and the Preanalytical Phase Working Group of the EFLM Science Committee
van der Molen AJ, Krabbe JG, Dekkers IA, Geenen RWF, Bellin MF, Bertolotto M, Brismar TB, Cadamuro J, Correas JM, Heinz-Peer G, Langlois MR, Mahnken AH, Ozben T, Quattrocchi CC, Radbruch A, Reimer P, Roditi G, Romanini L, Sebastià C, Simundic AM, Stacul F, Clement O.

The Contrast Media Safety Committee of the European Society of Urogenital Radiology has, together with the Preanalytical Phase Working Group of the EFLM Science Committee, reviewed the literature and updated its recommendations to increase awareness and provide insight into these interferences. CLINICAL RELEVANCE STATEMENT: Contrast Media may interfere with clinical laboratory tests. Awareness of potential interference may prevent unwanted misdiagnosis. KEY POINTS: • Contrast Media may interfere with clinical laboratory tests; therefore awareness of potential interference may prevent unwanted misdiagnosis. • Clinical Laboratory tests should be performed prior to radiological imaging with contrast media or alternatively, blood or urine collection should be delayed, depending on kidney function.

Gepubliceerd: Eur Radiol. 2023.
Impact factor: 5.9 ; Q1

Totale impact factor: 13.7
Gemiddelde impact factor: 4.6

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

Klinische farmacie

1. Discontinuation of infliximab treatment in patients with inflammatory bowel disease who retransitioned to originator and those who remained on biosimilar
Meijboom RW, Gardarsdottir H, Becker ML, Movig KLL, Kuijvenhoven J, Egberts TCG, Giezen TJ.

Background: Many patients with inflammatory bowel disease (IBD) have transitioned from an infliximab originator to a biosimilar. However, some patients retransition to the originator (i.e. stop biosimilar and reinitiate the originator). Whether this sign of potential unsatisfactory treatment response is specifically related to the infliximab biosimilar or the patient and/or the disease including patients' beliefs on the biosimilar is unclear.
Objectives: We aimed to compare the risk of and reasons for infliximab discontinuation between retransitioned patients and those remaining on biosimilar.
Design: Non-interventional, multicentre cohort study.
Methods: IBD patients who transitioned from infliximab originator to biosimilar between January 2015 and September 2019 in two Dutch hospitals were eligible for this study. Retransitioned patients (retransitioning cohort) were matched with patients remaining on biosimilar (biosimilar remainder cohort). Reasons for discontinuation were categorised as the unwanted response (i.e. loss of effect or adverse events) or remission. Risk of unwanted discontinuation was compared using Cox proportional hazards models.
Results: Patients in the retransitioning cohort (*n* = 44) were younger (median age 39.9 *versus* 44.0 years), more often female (65.9% *versus* 48.9%) and had shorter dosing intervals (median 48.5 *versus* 56.0 days) than in the biosimilar remainder cohort (*n* = 127). Infliximab discontinuation due to unwanted response was 22.7% in the retransitioning and 13.4% in the biosimilar remainder cohort, and due to remission was 2.3% and 9.4%, respectively. Retransitioned patients are at increased risk of discontinuing due to unwanted response compared with biosimilar remainder patients (adjusted HR 3.7, 95% CI: 1.0-13.9). Patients who retransitioned due to an increase in objective disease markers had higher discontinuation rates than patients who retransitioned due to symptoms only (66.7% *versus* 23.7%).
Conclusion: Retransitioned patients are at increased risk of infliximab discontinuation due to unwanted response. Retransitioning appeared related to the patient and/or disease and not the product. Clinicians might switch patients opting for retransitioning to other treatment regimens.

Gepubliceerd: Therap Adv Gastroenterol. 2023;16:17562848231197923.
Impact factor: 4.2 ; Q2

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2. Cost-utility analysis of a structured medication review compared to usual care in Parkinson's disease
Oonk NGM, Dorresteijn LDA, van den Berg AD, van der Palen J, Movig KLL, Nijmeijer HW, van Kesteren ME, Koffijberg H.

Purpose: For controlling symptoms in Parkinson's disease (PD) together with treating additional comorbidities, patients often face complex medication regimens, with suboptimal adherence, drug-related problems, and diminished therapy efficacy as a common consequence. A medication review could potentially tackle these issues, among others by optimizing drug treatment. Even if no change in clinical outcomes is observed, this intervention might decrease health care costs by reducing drug-related problems and hospital admissions. This study aimed to gain more insight in the health benefits and costs of a structured medication review (SMR) in PD.
Methods: A cost-utility analysis was performed, based on a multicenter randomized controlled trial with 202 PD patients with polypharmacy. The intervention group received an SMR, whereas the

control group received usual care. The intervention effect after 6 months of follow-up was presented as incremental quality-adjusted life years (QALY) using the EQ-5D-5L questionnaire. Costs were based on real-world data. Missing data was imputed using multiple imputation techniques. Bootstrapping was used to estimate the uncertainty in all health and economic outcomes.
Results: The QALY gain in the intervention group compared to the control group was - 0.011 (95% CI - 0.043; 0.020). Incremental costs were €433 (95% CI - 873; 1687). When adapting a willingness-to-pay threshold of €20,000/QALY and €80,000/QALY, the probability of SMRs being cost-effective was 18% and 30%, respectively.
Conclusion: A community pharmacist-led SMR in PD patients in the current setting shows no apparent benefit and is not cost-effective after 6 months, compared to usual care.
Trial registration: Netherlands Trial Register, NL4360. Registered 17 March 2014.

Gepubliceerd: Eur J Clin Pharmacol. 2023;79(2):289-97.
Impact factor: 2.9 ; Q3

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3. Acute kidney injury associated with nephrotoxic drugs in critically ill patients: a multicenter cohort study using electronic health record data
Yasrebi-de Kom IAR, Dongelmans DA, Abu-Hanna A, Schut MC, de Lange DW, van Roon EN, de Jonge E, Bouman CSC, de Keizer NF, Jager KJ, Klopotowska JE, RESCUE Study Group: Beishuizen A, Vermeijden JW, Masselink JB.

Background: Nephrotoxic drugs frequently cause acute kidney injury (AKI) in adult intensive care unit (ICU) patients. However, there is a lack of large pharmaco-epidemiological studies investigating the associations between drugs and AKI. Importantly, AKI risk factors may also be indications or contraindications for drugs and thereby confound the associations. Here, we aimed to estimate the associations between commonly administered (potentially) nephrotoxic drug groups and AKI in adult ICU patients whilst adjusting for confounding.
Methods: In this multicenter retrospective observational study, we included adult ICU admissions to 13 Dutch ICUs. We measured exposure to 44 predefined (potentially) nephrotoxic drug groups. The outcome was AKI during ICU admission. The association between each drug group and AKI was estimated using etiological cause-specific Cox proportional hazard models and adjusted for confounding. To facilitate an (independent) informed assessment of residual confounding, we manually identified drug group-specific confounders using a large drug knowledge database and existing literature.
Results: We included 92 616 ICU admissions, of which 13 492 developed AKI (15%). We found 14 drug groups to be associated with a higher hazard of AKI after adjustment for confounding. These groups included established (e.g. aminoglycosides), less well established (e.g. opioids) and controversial (e.g. sympathomimetics with α- and β-effect) drugs.
Conclusions: The results confirm existing insights and provide new ones regarding drug associated AKI in adult ICU patients. These insights warrant caution and extra monitoring when prescribing nephrotoxic drugs in the ICU and indicate which drug groups require further investigation.

Gepubliceerd: Clin Kidney J. 2023;16(12):2549-58.
Impact factor: 4.6 ; Q1

Totale impact factor: 11.7
Gemiddelde impact factor: 3.9

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 0

Totale impact factor: NVT
Gemiddelde impact factor: NVT

Klinische psychologie

1. Cognition, emotional state, and quality of life of survivors after cardiac arrest with rhythmic and periodic EEG patterns
van Gils PCW, Ruijter BJ, Bloo RJK, van Putten M, Foudraine NA, van Hout MSE, Tromp SC, van Mook W, Rouhl RPW, van Heugten CM, Hofmeijer J.

Aim: Rhythmic and periodic patterns (RPPs) on the electroencephalogram (EEG) in comatose patients after cardiac arrest have been associated with high case fatality rates. A good neurological outcome according to the Cerebral Performance Categories (CPC) has been reported in up to 10% of cases. Data on cognitive, emotional, and quality of life outcomes are lacking. We aimed to provide insight into these outcomes at one-year follow-up.
METHODS: We assessed outcome of surviving comatose patients after cardiac arrest with RPPs included in the 'treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation' (TELSTAR) trial at one-year follow-up, including the CPC for functional neurological outcome, a cognitive assessment, the hospital anxiety and depression scale (HADS) for emotional outcomes, and the 36-item short-form health survey (SF-36) for quality of life. Cognitive impairment was defined as a score of more than 1.5 SD below the mean on ≥ 2 (sub)tests within a cognitive domain.
RESULTS: Fourteen patients were included (median age 58 years, 21% female), of whom 13 had a cognitive impairment. Eleven of 14 were impaired in memory, 9/14 in executive functioning, and 7/14 in attention. The median scores on the HADS and SF-36 were all worse than expected. Based on the CPC alone, 8/14 had a good outcome (CPC 1-2).
CONCLUSION: Nearly all cardiac arrest survivors with RPPs during the comatose state have cognitive impairments at one-year follow-up. The incidence of anxiety and depression symptoms seem relatively high and quality of life relatively poor, despite 'good' outcomes according to the CPC.

Gepubliceerd: Resuscitation. 2023;189:109830.
Impact factor: 6.5 ; Q1

Totale impact factor: 6.5
Gemiddelde impact factor: 6.5

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 0
Totale impact factor: NVT
Gemiddelde impact factor: NVT

KNO

1. Patients' and Healthcare Professionals' Perspectives on Better Use of Patient-Reported Outcome Measures in Head and Neck Cancer
de Jel DVC, Young-Afat DA, Ooms-Renckens MM, Smeele LE, Rakhorst HA, DHNA study group: van Bemmel AJM

Objectives: Patients with head and neck cancer (HNC) are often highly affected by disease and treatment, resulting in impaired physical functioning and quality of life. Therefore, evaluation of patients' psychosocial and functional outcomes can be facilitated by patient-reported outcome measures (PROMs). By providing the patients' own perspectives, PROMs are crucial to improving patient-centered care. This study aimed to improve understanding of the perceived value of PROMs in HNC care and how to optimize their clinical value based on patients' and multidisciplinary healthcare professionals' (HCPs) perspectives.
Methods: Population-based surveys among patients with HNC through their patient association and among HCPs nationwide through the Dutch Head and Neck Audit.
Results: A total of 54 patients and 40 multidisciplinary HCPs from all 14 nationwide HNC centers (100%) responded. For patients, the most important element of patient-reported outcome collection systems was including a call to action for those with worse-than-average scores (28%), whereas clinicians found discussing scores during clinical visits the most important (39%). Although 16% of clinicians found short completion time the most important element, none of the patients selected completion time as most important. Additionally, 17% of patients stated completion time was not an issue, provided clinicians would use the outcomes for clinical purposes.
Conclusions: Although patients and clinicians acknowledged the value of patient-reported outcomes, patients would like to be more involved in the clinical implications of their outcomes. Enhancing patients' involvement by a call to action and providing feedback on their scores during outpatient clinic visits may improve the clinical value of PROMs.

Gepubliceerd: Value Health. 2023;26(8):1210-6.
Impact factor: 4.5 ; Q1

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2. [Temporomandibular joint dysfunction as a result of a condylar metastasis]
Klijn RJ, Huizinga MP, van Bemmel AJM.

An 83-year-old man reported recent temporomandibular joint complaints and a swelling near his ear. The swelling moved whileopening the mouth. Additional imaging showed an osseous deviation of the right condyle with extension into the masticator space. In addition, several lytic and expansive bone lesions were visible in the skeleton, which initially suggested multiple myeloma. However, blood tests pointed in the direction of prostate cancer that had been treated twenty years earlier. There appeared to be extensive osseous metastatic recurrent prostate carcinoma with a metastasis in the right condyle of the mandible. The patient was treated with palliative systemic therapy.

Gepubliceerd: Ned Tijdschr Tandheelkd. 2023;130(4):161-4.
Impact factor: onbekend

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3. Mastoid obliteration with hydroxyapatite vs. bone pâté in mastoidectomy surgery performed on patients with cholesteatoma and chronic suppurative otitis media: a retrospective analysis
Lindeboom JJ, van Kempen PMW, Buwalda J, Westerlaken BO, van Zuijlen DA, Bom SJH, van der Beek FB.

PURPOSE: To compare the efficacy and safety of hydroxyapatite vs. bone pâté as obliteration material in mastoidectomy surgery for patients with chronic suppurative otitis media and cholesteatoma. METHODS: This is a retrospective, multi-center, cohort study. All patients were followed up with micro-otoscopy, audiometry, and, if indicated, MRI with diffusion-weighted imaging. The following outcome parameters were analyzed: procedure safety (wound infections and complications), cholesteatoma recidivism rates (residual/recurrent), control of infection (Merchant's scale), and hearing results (pure-tone averages at 500/1000/2000/4000 Hz). RESULTS: Eighty-three cases were included: 45 obliterated with hydroxyapatite and 38 with bone pâté, with a mean follow-up time of, respectively, 25 and 24 months. Wound infections were only detected in the bone pâté group (4.8%) and successfully treated with oral or intravenous antibiotics and surgical drainage ($p = 0.026$). No other major surgical complications were observed in both groups. Cholesteatoma recidivism was observed in 15% using hydroxyapatite and 12% using bone pâté ($p = 0.471$). Complete control of infection (Merchant 0) was achieved in 76.2% using bone pâté and 86.8% using hydroxyapatite at 12 months postoperatively ($p = 0.223$). All patients showed good postoperative healing without complete failure to manage infection (Merchant 3). Pre- and postoperative audiometry showed significant improvement in hearing results in both groups. No significant difference between the obliteration materials was observed. CONCLUSIONS: Evaluation of mastoid obliteration reveals that hydroxyapatite and bone pâté are safe and effective obliteration materials, with high success rates in achieving a dry ear, low recidivism rates, and good hearing outcome, respecting the short-term limitation. In addition, our study shows that hydroxyapatite results in fewer postoperative wound infections compared to bone pâté.

Gepubliceerd: Eur Arch Otorhinolaryngol. 2023;280(4):1703-11.
Impact factor: 2.6 ; Q2

Totale impact factor: 7.1
Gemiddelde impact factor: 2.4

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 3
Totale impact factor: 7.1
Gemiddelde impact factor: 2.4

Longgeneeskunde

1. Implementation of Recommendations on the Use of Corticosteroids in Severe COVID-19
Camirand-Lemyre F, Merson L, Tirupakuzhi Vijayaraghavan BK, Burrell AJC, Citarella BW, Domingue MP, Lévesque S, Usuf E, Wils EJ, Ohshimo S, Martin-Loeches I, Sandulescu O, Laake JH, Lamontagne F, ISARIC Clinical Characterisation 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.

Importance: Research diversity and representativeness are paramount in building trust, generating valid biomedical knowledge, and possibly in implementing clinical guidelines.
Objectives: To compare variations over time and across World Health Organization (WHO) geographic regions of corticosteroid use for treatment of severe COVID-19; secondary objectives were to evaluate the association between the timing of publication of the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial (June 2020) and the WHO guidelines for corticosteroids (September 2020) and the temporal trends observed in corticosteroid use by region and to describe the geographic distribution of the recruitment in clinical trials that informed the WHO recommendation.
Design, setting, and participants: This prospective cohort study of 434 851 patients was conducted between January 31, 2020, and September 2, 2022, in 63 countries worldwide. The data were collected under the auspices of the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC)-WHO Clinical Characterisation Protocol for Severe Emerging Infections. Analyses were restricted to patients hospitalized for severe COVID-19 (a subset of the ISARIC data set).
Exposure: Corticosteroid use as reported to the ISARIC-WHO Clinical Characterisation Protocol for Severe Emerging Infections.
Main outcomes and measures: Number and percentage of patients hospitalized with severe COVID-19 who received corticosteroids by time period and by WHO geographic region.
Results: Among 434 851 patients with confirmed severe or critical COVID-19 for whom receipt of corticosteroids could be ascertained (median [IQR] age, 61.0 [48.0-74.0] years; 53.0% male), 174 307 (40.1%) received corticosteroids during the study period. Of the participants in clinical trials that informed the guideline, 91.6% were recruited from the United Kingdom. In all regions, corticosteroid use for severe COVID-19 increased, but this increase corresponded to the timing of the RECOVERY trial (time-interruption coefficient 1.0 [95% CI, 0.9-1.2]) and WHO guideline (time-interruption coefficient 1.9 [95% CI, 1.7-2.0]) publications only in Europe. At the end of the study period, corticosteroid use for treatment of severe COVID-19 was highest in the Americas (5421 of 6095 [88.9%]; 95% CI, 87.7-90.2) and lowest in Africa (31 588 of 185 191 [17.1%]; 95% CI, 16.8-17.3).
Conclusions and relevance: The results of this cohort study showed that implementation of the guidelines for use of corticosteroids in the treatment of severe COVID-19 varied geographically. Uptake of corticosteroid treatment was lower in regions with limited clinical trial involvement. Improving research diversity and representativeness may facilitate timely knowledge uptake and guideline implementation.

Gepubliceerd: JAMA Netw Open. 2023;6(12):e2346502.
Impact factor: 13.8 ; Q1

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2. Neurological manifestations of COVID-19 in adults and children
Cho SM, White N, Premraj L, Battaglini D, Fanning J, Suen J, Bassi GL, Fraser J, Robba C, Griffee M, Singh B, Citarella BW, Merson L, Solomon T, Thomson D, ISARIC Clinical Characterisation 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.

Different neurological manifestations of coronavirus disease 2019 (COVID-19) in adults and children and their impact have not been well characterized. We aimed to determine the prevalence of neurological manifestations and in-hospital complications among hospitalized COVID-19 patients and ascertain differences between adults and children. We conducted a prospective multicentre observational study using the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) cohort across 1507 sites worldwide from 30 January 2020 to 25 May 2021. Analyses of neurological manifestations and neurological complications considered unadjusted prevalence estimates for predefined patient subgroups, and adjusted estimates as a function of patient age and time of hospitalization using generalized linear models. Overall, 161 239 patients (158 267 adults; 2972 children) hospitalized with COVID-19 and assessed for neurological manifestations and complications were included. In adults and children, the most frequent neurological manifestations at admission were fatigue (adults: 37.4%; children: 20.4%), altered consciousness (20.9%; 6.8%), myalgia (16.9%; 7.6%), dysgeusia (7.4%; 1.9%), anosmia (6.0%; 2.2%) and seizure (1.1%; 5.2%). In adults, the most frequent in-hospital neurological complications were stroke (1.5%), seizure (1%) and CNS infection (0.2%). Each occurred more frequently in intensive care unit (ICU) than in non-ICU patients. In children, seizure was the only neurological complication to occur more frequently in ICU versus non-ICU (7.1% versus 2.3%, $P < 0.001$). Stroke prevalence increased with increasing age, while CNS infection and seizure steadily decreased with age. There was a dramatic decrease in stroke over time during the pandemic. Hypertension, chronic neurological disease and the use of extracorporeal membrane oxygenation were associated with increased risk of stroke. Altered consciousness was associated with CNS infection, seizure and stroke. All in-hospital neurological complications were associated with increased odds of death. The likelihood of death rose with increasing age, especially after 25 years of age. In conclusion, adults and children have different neurological manifestations and in-hospital complications associated with COVID-19. Stroke risk increased with increasing age, while CNS infection and seizure risk decreased with age.

Gepubliceerd: Brain. 2023;146(4):1648-61.
Impact factor: 14.5 ; Q1

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3. Regional peak flow as a novel approach to assess regional pulmonary mechanics by electrical impedance tomography: an observational validation study
de Jongh SAM, Heines SJH, de Jongh FHC, Segers RPJ, van der Horst ICC, van Bussel BCT, Bergmans D.

Background: Spontaneous breathing efforts during mechanical ventilation are a widely accepted weaning approach for acute respiratory distress syndrome (ARDS) patients. These efforts can be too vigorous, possibly inflicting lung and diaphragm damage. Higher positive end expiratory pressure (PEEP) levels can be used to lower the magnitude of vigorous breathing efforts. Nevertheless, PEEP titrating tools are lacking in spontaneous mechanical ventilation (SMV). Therefore, the aim is to develop an electrical impedance tomography (EIT) algorithm for quantifying regional lung mechanics independent from a stable plateau pressure phase based on regional peak flow (RPF) by EIT, which is hypothetically applicable in SMV and to validate this algorithm in patients on controlled mechanical ventilation (CMV).
Methods: The RPF algorithm quantifies a cumulative overdistension (OD_{RPF}) and collapse (CL_{RPF}) rate and is validated in a prospective cohort of mechanically ventilated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patients on CMV. OD_{RPF} and CL_{RPF} are compared with compliance-based cumulative overdistension (OD_{P500}) and collapse (CL_{P500}) rates from the Pulmovista 500 EIT device at multiple PEEP levels (PEEP 10 cmH_2O to PEEP 24 cmH_2O) in EIT measurements from CMV patients by linear mixed models, Bland-Altman analysis and intraclass correlation coefficient (ICC).
Results: Seventy-eight patients were included. Linear mixed models revealed an association between OD_{RPF} and OD_{P500} of 1.02 (0.98-1.07, P<0.001) and between CL_{RPF} and CL_{P500} of 0.93 (0.80-1.05, P<0.001). ICC values ranged from 0.78 to 0.86 (P<0.001) for OD_{RPF} and OD_{P500} and from 0.70 to 0.85

(P<0.001) for CL_{RPF} and CL_{P500} (PEEP 10 to PEEP 24). The mean bias between OD_{RPF} and OD_{P500} in these PEEP levels ranged from 0.80% to 4.19% and from -1.31% to 0.13% between CL_{RPF} and CL_{P500}. **Conclusions:** A RPF approach for quantifying regional lung mechanics showed a moderate to good agreement in coronavirus disease 2019 (COVID-19) related ARDS patients on CMV compared to the compliance-based approach. This, in addition to being independent of a plateau pressure phase, indicates that the RPF approach is a valid method to explore for quantifying regional lung mechanics in SMV.

Gepubliceerd: Ann Transl Med. 2023;11(6):253.
Impact factor: 3.6 ; Q3 *2021

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4. Evaluation of Exacerbation and Symptom-Free Time in Patients with COPD
de Vries MI, Effing TW, van der Palen J, Schrijver J, van der Valk P, Lenferink A.

In clinical practice, clinicians mainly focus on Chronic Obstructive Pulmonary Disease (COPD) exacerbations and symptoms, while patients may prefer to evaluate periods free of COPD exacerbations and deteriorated symptoms. The latter would suit the positive health approach that centralizes people and their beliefs. We aimed to identify patient characteristics and health outcomes relating to: 1) COPD exacerbation-free days; 2) days with no more symptoms than usual; and 3) combined COPD exacerbation and comorbid flare-up-free days (i.e. chronic heart failure, anxiety, depression flare-ups) using negative binomial regression analyzes. Data were obtained from two self-management intervention trials including COPD patients with and without comorbidities. 313 patients (mean age 66.0 years, 63.6% male, 68.7% comorbidity) were included. Better baseline chronic respiratory questionnaire (CRQ) fatigue (incidence rate ratio (IRR) = 1.03 (95% CI 1.01-1.05), p = 0.02) and mastery scores (IRR = 1.03 (95% CI 1.00-1.06), p = 0.04) and fewer courses of antibiotics (IRR = 0.95 (95% CI 0.94-0.96), p < 0.01) were related to more COPD exacerbation-free days. Additionally, better baseline CRQ fatigue (IRR = 1.05 (95% CI 1.00-1.10), p = 0.04) and mastery scores (IRR = 1.06 (95% CI 1.00-1.12), p = 0.04), fewer courses of antibiotics (IRR = 0.94 (95% CI 0.91-0.96), p < 0.01), and improved CRQ dyspnea scores over 12 months of follow-up (IRR = 1.07 (95% CI 1.01-1.12), p < 0.01) were correlated to more days free of deteriorated symptoms. Less baseline dyspnea (modified Medical Research Council score) (IRR = 0.95 (95% CI 0.92-0.98), p < 0.01) and fewer courses of antibiotics (IRR = 0.94 (95% CI 0.93-0.95), p < 0.01) were associated with more combined COPD exacerbation and comorbid flare-up-free days. Healthcare professionals should be aware that less fatigue and better mastering of COPD relate to more exacerbation and symptom-free time in COPD patients.

Gepubliceerd: Copd. 2023;20(1):9-17.
Impact factor: 2.2 ; Q4

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5. Prospective Detection of Early Lung Cancer in Patients With COPD in Regular Care by Electronic Nose Analysis of Exhaled Breath
de Vries R, Farzan N, Fabius T, De Jongh FHC, Jak PMC, Haarman EG, Snoey E, In 't Veen J, Dagelet YWF, Maitland-Van Der Zee AH, Lucas A, Van Den Heuvel MM, Wolf-Lansdorf M, Muller M, Baas P, Sterk PJ.

Background: Patients with COPD are at high risk of lung cancer developing, but no validated predictive biomarkers have been reported to identify these patients. Molecular profiling of exhaled breath by electronic nose (eNose) technology may qualify for early detection of lung cancer in patients with COPD.

Research question: Can eNose technology be used for prospective detection of early lung cancer in patients with COPD?
Study design and methods: BreathCloud is a real-world multicenter prospective follow-up study using diagnostic and monitoring visits in day-to-day clinical care of patients with a standardized diagnosis of asthma, COPD, or lung cancer. Breath profiles were collected at inclusion in duplicate by a metal-oxide semiconductor eNose positioned at the rear end of a pneumotachograph (SpiroNose; Breathomix). All patients with COPD were managed according to standard clinical care, and the incidence of clinically diagnosed lung cancer was prospectively monitored for 2 years. Data analysis involved advanced signal processing, ambient air correction, and statistics based on principal component (PC) analysis, linear discriminant analysis, and receiver operating characteristic analysis.
Results: Exhaled breath data from 682 patients with COPD and 211 patients with lung cancer were available. Thirty-seven patients with COPD (5.4%) demonstrated clinically manifest lung cancer within 2 years after inclusion. Principal components 1, 2, and 3 were significantly different between patients with COPD and those with lung cancer in both training and validation sets with areas under the receiver operating characteristic curve of 0.89 (95% CI, 0.83-0.95) and 0.86 (95% CI, 0.81-0.89). The same three PCs showed significant differences ($P < .01$) at baseline between patients with COPD who did and did not subsequently demonstrate lung cancer within 2 years, with a cross-validation value of 87% and an area under the receiver operating characteristic curve of 0.90 (95% CI, 0.84-0.95).
Interpretation: Exhaled breath analysis by eNose identified patients with COPD in whom lung cancer became clinically manifest within 2 years after inclusion. These results show that eNose assessment may detect early stages of lung cancer in patients with COPD.

Gepubliceerd: Chest. 2023;164(5):1315-24.
Impact factor: 10.1 ; Q1

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6. Implications of the new ERS/ATS standards on the interpretation of lung function tests
Desbordes P, De Vos M, Maes J, de Jongh F, Sylvester K, Vogelmeier CF, Dinh-Xuan AT, Mortensen J, Janssens W, Topalovic M.

Gepubliceerd: Eur Respir J. 2023;61(3).
Impact factor: 24.9 ; Q1

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7. Effort and work-of-breathing parameters strongly correlate with increased resistance in an animal model
Flink RC, Newth CJL, Hotz JC, Kneyber MCJ, Ross PA, de Jongh FH, van Kaam AH, Khemani RG.

Background: Effort of Breathing (EOB) calculations may be a reliable alternative to Work of Breathing (WOB) calculations in which Respiratory Inductance Plethysmography (RIP) replaces spirometry. We sought to compare EOB and WOB measurements in a nonhuman primate model of increasing extrathoracic inspiratory resistance simulating upper airway obstruction (UAO).
Methods: RIP, spirometry, and esophageal manometry were measured in spontaneously breathing, intubated Rhesus monkeys utilizing 11 calibrated resistors randomly applied for 2-min. EOB was calculated breath-by-breath as Pressure Rate Product (PRP) and Pressure Time Product (PTP). WOB was calculated from the Pressure-Volume curve based on spirometry (WOB_{SPIR}) or RIP flow (WOB_{RIP}).
Results: WOB, PRP and PTP showed similar linear increases when exposed to higher levels of resistive loads. When comparing WOB_{SPIR} to WOB_{RIP}, a similar strong correlation was seen for both signals as resistance increased and there were no statistically significant differences.
Conclusion: EOB and WOB parameters utilizing esophageal manometry and RIP, independent of spirometry, showed a strong correlation as a function of increasing inspiratory resistance in

nonhuman primates. This allows several potential monitoring possibilities for non-invasively ventilated patients or situations where spirometry is not available.
Impact: EOB and WOB parameters showed a strong correlation as a function of increasing inspiratory resistance in nonhuman primates. There was a strong correlation between spirometry-based WOB versus RIP-based WOB. To date, it has remained untested as to whether EOB is a reliable alternative for WOB and if RIP can replace spirometry in these measurements. Our results enable additional potential monitoring possibilities for non-invasively ventilated patients or situations where spirometry is not available. Where spirometry is not available, there is no need to apply a facemask post extubation to a spontaneously breathing, non-intubated infant to make objective EOB measurements.

Gepubliceerd: Pediatr Res. 2023;94(3):944-9.
Impact factor: 3.6 ; Q1

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8. Thrombotic and hemorrhagic complications of COVID-19 in adults hospitalized in high-income countries compared with those in adults hospitalized in low- and middle-income countries in an international registry
Griffee MJ, Bozza PT, Reyes LF, Eddington DP, Rosenberger D, Merson L, Citarella BW, Fanning JP, Alexander PMA, Fraser J, Dalton H, Cho SM, ISARIC Clinical Characterisation 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: COVID-19 has been associated with a broad range of thromboembolic, ischemic, and hemorrhagic complications (coagulopathy complications). Most studies have focused on patients with severe disease from high-income countries (HICs).
Objectives: The main aims were to compare the frequency of coagulopathy complications in developing countries (low- and middle-income countries [LMICs]) with those in HICs, delineate the frequency across a range of treatment levels, and determine associations with in-hospital mortality.
Methods: Adult patients enrolled in an observational, multinational registry, the International Severe Acute Respiratory and Emerging Infections COVID-19 study, between January 1, 2020, and September 15, 2021, met inclusion criteria, including admission to a hospital for laboratory-confirmed, acute COVID-19 and data on complications and survival. The advanced-treatment cohort received care, such as admission to the intensive care unit, mechanical ventilation, or inotropes or vasopressors; the basic-treatment cohort did not receive any of these interventions.
Results: The study population included 495,682 patients from 52 countries, with 63% from LMICs and 85% in the basic treatment cohort. The frequency of coagulopathy complications was higher in HICs (0.76%-3.4%) than in LMICs (0.09%-1.22%). Complications were more frequent in the advanced-treatment cohort than in the basic-treatment cohort. Coagulopathy complications were associated with increased in-hospital mortality (odds ratio, 1.58; 95% CI, 1.52-1.64). The increased mortality associated with these complications was higher in LMICs (58.5%) than in HICs (35.4%). After controlling for coagulopathy complications, treatment intensity, and multiple other factors, the mortality was higher among patients in LMICs than among patients in HICs (odds ratio, 1.45; 95% CI, 1.39-1.51).
Conclusion: In a large, international registry of patients hospitalized for COVID-19, coagulopathy complications were more frequent in HICs than in LMICs (developing countries). Increased mortality associated with coagulopathy complications was of a greater magnitude among patients in LMICs. Additional research is needed regarding timely diagnosis of and intervention for coagulation derangements associated with COVID-19, particularly for limited-resource settings.

Gepubliceerd: Res Pract Thromb Haemost. 2023;7(5):102142.
Impact factor: 4.6 ; Q2

9. Characteristics and outcomes of an international cohort of 600 000 hospitalized patients with COVID-19

Kartsonaki C, Baillie JK, Barrio NG, Baruch J, Beane A, Blumberg L, Bozza F, Broadley T, Burrell A, Carson G, Citarella BW, Dagens A, Dankwa EA, Donnelly CA, Dunning J, Elotmani L, Escher M, Farshait N, Goffard JC, Gonçalves BP, Hall M, Hashmi M, Sim Lim Heng B, Ho A, Jassat W, Pedrera Jiménez M, Laouenan C, Lissauer S, Martin-Loeches I, Mentré F, Merson L, Morton B, Munblit D, Nekliudov NA, Nichol AD, Singh Oinam BC, Ong D, Panda PK, Petrovic M, Pritchard MG, Ramakrishnan N, Ramos GV, Roger C, Sandulescu O, Semple MG, Sharma P, Sigfrid L, Somers EC, Streinu-Cercel A, Taccone F, Vecham PK, Kumar Tirupakuzhi Vijayaraghavan B, Wei J, Wils EJ, Ci Wong X, Horby P, Rojek A, Olliaro PL, ISARIC Clinical Characterisation 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: We describe demographic features, treatments and clinical outcomes in the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) COVID-19 cohort, one of the world's largest international, standardized data sets concerning hospitalized patients.
Methods: The data set analysed includes COVID-19 patients hospitalized between January 2020 and January 2022 in 52 countries. We investigated how symptoms on admission, co-morbidities, risk factors and treatments varied by age, sex and other characteristics. We used Cox regression models to investigate associations between demographics, symptoms, co-morbidities and other factors with risk of death, admission to an intensive care unit (ICU) and invasive mechanical ventilation (IMV).
Results: Data were available for 689 572 patients with laboratory-confirmed (91.1%) or clinically diagnosed (8.9%) SARS-CoV-2 infection from 52 countries. Age [adjusted hazard ratio per 10 years 1.49 (95% CI 1.48, 1.49)] and male sex [1.23 (1.21, 1.24)] were associated with a higher risk of death. Rates of admission to an ICU and use of IMV increased with age up to age 60 years then dropped. Symptoms, co-morbidities and treatments varied by age and had varied associations with clinical outcomes. The case-fatality ratio varied by country partly due to differences in the clinical characteristics of recruited patients and was on average 21.5%.
Conclusions: Age was the strongest determinant of risk of death, with a ∼30-fold difference between the oldest and youngest groups; each of the co-morbidities included was associated with up to an almost 2-fold increase in risk. Smoking and obesity were also associated with a higher risk of death. The size of our international database and the standardized data collection method make this study a comprehensive international description of COVID-19 clinical features. Our findings may inform strategies that involve prioritization of patients hospitalized with COVID-19 who have a higher risk of death.

Gepubliceerd: Int J Epidemiol. 2023;52(2):355-76.
Impact factor: 7.7 ; Q1

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10. Diagnosing Non-Small Cell Lung Cancer by Exhaled Breath Profiling Using an Electronic Nose: A Multicenter Validation Study

Kort S, Brusse-Keizer M, Schouwink H, Citgez E, de Jongh FH, van Putten JWG, van den Borne B, Kastelijn EA, Stolz D, Schuurbiers M, van den Heuvel MM, van Geffen WH, van der Palen J.

ackground: Despite the potential of exhaled breath analysis of volatile organic compounds to diagnose lung cancer, clinical implementation has not been realized, partly due to the lack of validation studies.
Research question: This study addressed two questions. First, can we simultaneously train and validate a prediction model to distinguish patients with non-small cell lung cancer from non-lung

cancer subjects based on exhaled breath patterns? Second, does addition of clinical variables to exhaled breath data improve the diagnosis of lung cancer?
Study design and methods: In this multicenter study, subjects with non-small cell lung cancer and control subjects performed 5 min of tidal breathing through the aeoNose, a handheld electronic nose device. A training cohort was used for developing a prediction model based on breath data, and a blinded cohort was used for validation. Multivariable logistic regression analysis was performed, including breath data and clinical variables, in which the formula and cutoff value for the probability of lung cancer were applied to the validation data.
Results: A total of 376 subjects formed the training set, and 199 subjects formed the validation set. The full training model (including exhaled breath data and clinical parameters from the training set) were combined in a multivariable logistic regression analysis, maintaining a cut off of 16% probability of lung cancer, resulting in a sensitivity of 95%, a specificity of 51%, and a negative predictive value of 94%; the area under the receiver-operating characteristic curve was 0.87. Performance of the prediction model on the validation cohort showed corresponding results with a sensitivity of 95%, a specificity of 49%, a negative predictive value of 94%, and an area under the receiver-operating characteristic curve of 0.86.
Interpretation: Combining exhaled breath data and clinical variables in a multicenter, multi-device validation study can adequately distinguish patients with lung cancer from subjects without lung cancer in a noninvasive manner. This study paves the way to implement exhaled breath analysis in the daily practice of diagnosing lung cancer.

Gepubliceerd: Chest. 2023;163(3):697-706.
Impact factor: 10.1 ; Q1

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11. Severe Asthma Standard-of-Care Background Medication Reduction With Benralizumab: ANDHI in Practice Substudy
Louis R, Harrison TW, Chanez P, Menzella F, Philteos G, Cosio BG, Lugogo NL, de Luiz G, Burden A, Adlington T, Keeling N, Kwiatek J, Garcia Gil E, ANDHI Study Investigators: van Veen H.

Background: The phase IIIb, randomized, parallel-group, placebo-controlled ANDHI double-blind (DB) study extended understanding of the efficacy of benralizumab for patients with severe eosinophilic asthma. Patients from ANDHI DB could join the 56-week ANDHI in Practice (IP) single-arm, open-label extension substudy.
Objective: Assess potential for standard-of-care background medication reductions while maintaining asthma control with benralizumab.
Methods: Following ANDHI DB completion, eligible adults were enrolled in ANDHI IP. After an 8-week run-in with benralizumab, there were 5 visits to potentially reduce background asthma medications for patients achieving and maintaining protocol-defined asthma control with benralizumab. Main outcome measures for non-oral corticosteroid (OCS)-dependent patients were the proportions with at least 1 background medication reduction (ie, lower inhaled corticosteroid dose, background medication discontinuation) and the number of adapted Global Initiative for Asthma (GINA) step reductions at end of treatment (EOT). Main outcomes for OCS-dependent patients were reductions in daily OCS dosage and proportion achieving OCS dosage of 5 mg or lower at EOT.
Results: For non-OCS-dependent patients, 53.3% (n = 208 of 390) achieved at least 1 background medication reduction, increasing to 72.6% (n = 130 of 179) for patients who maintained protocol-defined asthma control at EOT. A total of 41.9% (n = 163 of 389) achieved at least 1 adapted GINA step reduction, increasing to 61.8% (n = 110 of 178) for patients with protocol-defined EOT asthma control. At ANDHI IP baseline, OCS dosages were 5 mg or lower for 40.4% (n = 40 of 99) of OCS-dependent patients. Of OCS-dependent patients, 50.5% (n = 50 of 99) eliminated OCS and 74.7% (n = 74 of 99) achieved dosages of 5 mg or lower at EOT.

Conclusions: These findings demonstrate benralizumab's ability to improve asthma control, thereby allowing background medication reduction.

Gepubliceerd: J Allergy Clin Immunol Pract. 2023;11(6):1759-70.e7.
Impact factor: 9.4 ; Q1

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12. Influence of neonatal endotracheal tube dimensions on oscillometry-acquired reactance: a bench study
Pigmans R, van Leuteren RW, Scholten AWJ, Veneroni C, van Kaam AH, Hutten J, Dellacà RL, de Jongh FHC.

Objective: To examine the influence of the endotracheal tube (ETT) on respiratory reactance (X(rs)) measured with the forced oscillation technique (FOT) and develop a correction method for it.
Approach: In a bench study, the reactance of ETTs (X(tube)) with different dimensions was measured on a breathing test lung in various respiratory settings.
Main results: X(tube)can be accurately predicted by a fitted formula, with an R(2)of 0.97, with negligible effects due to changes in respiratory pattern and lung volume.
Significance: The developed formula offers the ability to measure ETT-independent X(rs)values of patients, improving the potential of FOT for lung function testing in mechanically ventilated newborns.

Gepubliceerd: Physiol Meas. 2023;44(1).
Impact factor: 3.2 ; Q2

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13. Transcutaneous electromyography as a tool to assess recovery of hemidiaphragmatic paresis: A case report
Scholten AWJ, van Leuteren RW, de Jongh FH, van Kaam AH, Markhorst DG, Hutten J.

In this case report, we describe two repeated transcutaneous electromyography of the diaphragm (dEMG) measurements in an infant with suspected paresis of the right hemidiaphragm after cardiac surgery. The first measurement, performed at the time of diagnosis, showed a lower electrical activity of the right side of the diaphragm in comparison with the left side. The second measurement, performed after a period of expectative management, showed that electrical activity of the affected side had increased and was similar to the activity of the left diaphragm. This finding was accompanied by an improvement in the clinical condition. In conclusion, repeated measurement of diaphragmatic activity using transcutaneous dEMG enables the observation and quantification of spontaneous recovery over time. This information may assist the clinician in identifying patients not responding to expectative management and in determining the optimal timing of diaphragmatic surgery.

Gepubliceerd: J Neonatal Perinatal Med. 2023;16(4):725-9.
Impact factor: onbekend

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14. Cardiorespiratory monitoring with a wireless and nonadhesive belt measuring diaphragm activity in preterm and term infants: A multicenter non-inferiority study
Scholten AWJ, Zhan Z, Niemarkt HJ, Vervoorn M, van Leuteren RW, de Jongh FH, van Kaam AH, Heuvel E, Hutten GJ.

Introduction: We determined if the heart rate (HR) monitoring performance of a wireless and nonadhesive belt is non-inferior compared to standard electrocardiography (ECG). Secondary objective was to explore the belt's respiratory rate (RR) monitoring performance compared to chest impedance (CI).
Method: In this multicenter non-inferiority trial, preterm and term infants were simultaneously monitored with the belt and conventional ECG/CI for 24 h. HR monitoring performance was estimated with the HR difference and ability to detect cardiac events compared to the ECG, and the incidence of HR-data loss per second. These estimations were statistically compared to prespecified margins to confirm equivalence/non-inferiority. Exploratory RR analyses estimated the RR trend difference and ability to detect apnea/tachypnea compared to CI, and the incidence of RR-data loss per second.
Results: Thirty-nine infants were included. HR monitoring with the belt was non-inferior to the ECG with a mean HR difference of 0.03 beats per minute (bpm) (standard error [SE] = 0.02) (95% limits of agreement [LoA]: [-5 to 5] bpm) ($p < 0.001$). Second, sensitivity and positive predictive value (PPV) for cardiac event detection were 94.0% (SE = 0.5%) and 92.6% (SE = 0.6%), respectively ($p \leq 0.001$). Third, the incidence of HR-data loss was 2.1% (SE = 0.4%) per second ($p < 0.05$). The exploratory analyses of RR showed moderate trend agreement with a mean RR-difference of 3.7 breaths/min (SE = 0.8) (LoA: [-12 to 19] breaths/min), but low sensitivities and PPV's for apnea/tachypnea detection. The incidence of RR-data loss was 2.2% (SE = 0.4%) per second.
Conclusion: The nonadhesive, wireless belt showed non-inferior HR monitoring and a moderate agreement in RR trend compared to ECG/CI. Future research on apnea/tachypnea detection is required.

Gepubliceerd: Pediatr Pulmonol. 2023;58(12):3574-81.
Impact factor: 3.1 ; Q2

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15. Facilitators and Barriers of Adherence to Multi-Disease Exacerbation Action Plans in COPD Patients - A Qualitative Study
Schrijver J, Effing T, Brusse-Keizer M, van der Palen J, van der Valk P, Lenferink A.

Whereas exacerbation action plans to self-manage Chronic Obstructive Pulmonary Disease (COPD) significantly improve health outcomes, patients' adherence to those action plans is often poor. This study aimed to identify facilitators and barriers of adherence to tailored multi-disease exacerbation action plans. We also explored patients' perspectives toward disease management roles. Individual semi-structured interviews were conducted with a sample of COPD patients who completed a Dutch-Australian self-management intervention evaluating tailored exacerbation action plans for COPD and relevant comorbidities. Interviews were thematically analyzed using a deductive approach guided by the Capability, Opportunity and Motivation of Behavior (COM-B) model. In 2016, ten patients (5 Australian; 5 Dutch; 6 men; age 59-83 years) were interviewed at the end of their one-year follow-up. Facilitators of adherence included improved patients' comprehension of disease and treatment, positive feelings about the intervention, improved self-confidence, and professional support. Barriers included difficulties to recognize symptoms, dislike toward daily symptom monitoring, negative feelings about the intervention, negative mood state, and complexity of symptom diaries and action plans. Patients indicated three distinctive perspectives of their own and their healthcare professional's role in their disease management: 1) patients felt mainly responsible; 2) patients felt shared responsibility with their healthcare professional; and 3) patients felt not responsible as they perceived their healthcare professional to be mainly responsible. We successfully used the COM-B model as a guide to identify facilitators and barriers of patients' adherence to multi-disease exacerbation action plans. Improving patients' adherence in future self-management interventions by targeting specific facilitators or barriers should be considered.

Gepubliceerd: Copd. 2023;20(1):262-73.
Impact factor: 2.2 ; Q4

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16. Exploring Patterns of COPD Exacerbations and Comorbid Flare-Ups
van Dijk SHB, Brusse-Keizer MGJ, Effing T, van der Valk P, Ploumen EH, van der Palen J, Doggen CJM, Lenferink A.

Background: Comorbidities are known to complicate disease management in patients with Chronic Obstructive Pulmonary Disease (COPD). This is partly due to lack of insight into the interplay of acute exacerbations of COPD (AECOPD) and comorbid flare-ups. This study aimed to explore patterns of AECOPDs and comorbid flare-ups.
Methods: Data of increased symptoms were extracted from a 12-month daily symptom follow-up database including patients with COPD and comorbidities (chronic heart failure (CHF), anxiety, depression) and transformed to visualizations of AECOPDs and comorbid flare-up patterns over time. Patterns were subsequently categorized using an inductive approach, based on both predominance (ie, which occurs most often) of AECOPDs or comorbid flare-ups, and their simultaneous (ie, simultaneous start in ≥ 50%) occurrence.
Results: We included 48 COPD patients (68 ± 9 years; comorbid CHF: 52%, anxiety: 40%, depression: 38%). In 25 patients with AECOPDs and CHF flare-ups, the following patterns were identified: AECOPDs predominant (n = 14), CHF flare-ups predominant (n = 5), AECOPDs nor CHF flare-ups predominant (n = 6). Of the 24 patients with AECOPDs and anxiety and/or depression flare-ups, anxiety and depression flare-ups occurred simultaneously in 15 patients. In 9 of these 24 patients, anxiety or depression flare-ups were observed independently from each other. In 31 of the included 48 patients, AECOPDs and comorbid flare-ups occurred mostly simultaneously.
Conclusion: Patients with COPD and common comorbidities show a variety of patterns of AECOPDs and comorbid flare-ups. Some patients, however, show repetitive patterns that could potentially be used to improve personalized disease management, if recognized.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis. 2023;18:2633-44.
Impact factor: 2.8 ; Q3

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17. Association of Country Income Level With the Characteristics and Outcomes of Critically Ill Patients Hospitalized With Acute Kidney Injury and COVID-19
Wainstein M, Spyrison N, Dai D, Ghadimi M, Chávez-Iñiguez JS, Rizo-Topete L, Citarella BW, Merson L, Pole JD, Claure-Del Granado R, Johnson DW, Shrapnel S, ISARIC Clinical Characterisation 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.

Introduction: Acute kidney injury (AKI) has been identified as one of the most common and significant problems in hospitalized patients with COVID-19. However, studies examining the relationship between COVID-19 and AKI in low- and low-middle income countries (LLMIC) are lacking. Given that AKI is known to carry a higher mortality rate in these countries, it is important to understand differences in this population.
Methods: This prospective, observational study examines the AKI incidence and characteristics of 32,210 patients with COVID-19 from 49 countries across all income levels who were admitted to an intensive care unit during their hospital stay.
Results: Among patients with COVID-19 admitted to the intensive care unit, AKI incidence was highest in patients in LLMIC, followed by patients in upper-middle income countries (UMIC) and high-income countries (HIC) (53%, 38%, and 30%, respectively), whereas dialysis rates were lowest among

patients with AKI from LLMIC and highest among those from HIC (27% vs. 45%). Patients with AKI in LLMIC had the largest proportion of community-acquired AKI (CA-AKI) and highest rate of in-hospital death (79% vs. 54% in HIC and 66% in UMIC). The association between AKI, being from LLMIC and in-hospital death persisted even after adjusting for disease severity.
Conclusions: AKI is a particularly devastating complication of COVID-19 among patients from poorer nations where the gaps in accessibility and quality of healthcare delivery have a major impact on patient outcomes.

Gepubliceerd: Kidney Int Rep. 2023;8(8):1514-30.
Impact factor: 6.0 ; Q1

Totale impact factor: 121.8
Gemiddelde impact factor: 7.2

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 5
Totale impact factor: 20.5
Gemiddelde impact factor: 4.1

MDL

1. Comparison of lumen-apposing metal stents versus double-pigtail plastic stents for infected necrotising pancreatitis
Boxhoorn L, Verdonk RC, Besselink MG, Boermeester M, Bollen TL, Bouwense SA, Cappendijk VC, Curvers WL, Dejong CH, van Dijk SM, van Dullemen HM, van Eijck CH, van Geenen EJ, Hadithi M, Hazen WL, Honkoop P, van Hooft JE, Jacobs MA, Kievits JE, Kop MP, Kouw E, Kuiken SD, Ledeboer M, Nieuwenhuijs VB, Perk LE, Poley JW, Quispel R, de Ridder RJ, van Santvoort HC, Sperna Weiland CJ, Stommel MW, Timmerhuis HC, Witteman BJ, Umans DS, Venneman NG, Vleggaar FP, van Wanrooij RL, Bruno MJ, Fockens P, Voermans RP.

Objective: Lumen-apposing metal stents (LAMS) are believed to clinically improve endoscopic transluminal drainage of infected necrosis when compared with double-pigtail plastic stents. However, comparative data from prospective studies are very limited.
Design: Patients with infected necrotising pancreatitis, who underwent an endoscopic step-up approach with LAMS within a multicentre prospective cohort study were compared with the data of 51 patients in the randomised TENSION trial who had been assigned to the endoscopic step-up approach with double-pigtail plastic stents. The clinical study protocol was otherwise identical for both groups. Primary end point was the need for endoscopic transluminal necrosectomy. Secondary end points included mortality, major complications, hospital stay and healthcare costs.
Results: A total of 53 patients were treated with LAMS in 16 hospitals during 27 months. The need for endoscopic transluminal necrosectomy was 64% (n=34) and was not different from the previous trial using plastic stents (53%, n=27)), also after correction for baseline characteristics (OR 1.21 (95% CI 0.45 to 3.23)). Secondary end points did not differ between groups either, which also included bleeding requiring intervention-5 patients (9%) after LAMS placement vs 11 patients (22%) after placement of plastic stents (relative risk 0.44; 95% CI 0.16 to 1.17). Total healthcare costs were also comparable (mean difference -€6348, bias-corrected and accelerated 95% CI -€26 386 to €10 121).
Conclusion: Our comparison of two patient groups from two multicentre prospective studies with a similar design suggests that LAMS do not reduce the need for endoscopic transluminal necrosectomy when compared with double-pigtail plastic stents in patients with infected necrotising pancreatitis. Also, the rate of bleeding complications was comparable.

Gepubliceerd: Gut. 2023;72(1):66-72.
Impact factor: 24.5 ; Q1

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2. Diagnostic potential of plasma biomarkers and exhaled volatile organic compounds in predicting the different stages of acute mesenteric ischaemia: protocol for a multicentre prospective observational study (TACTIC study)
Duivenvoorden AAM, Clarysse M, Ceulemans LJ, Geelkerken RH, Derikx JPM, de Vries JPM, Buscher H, Olde Damink SWM, van Schooten FJ, Lubbers T, Lenaerts K, Dutch Mesenteric Ischemia Study group: Kolkman, JJ.

Introduction: Acute mesenteric ischaemia (AMI) is a life-threatening condition with short-term mortality of up to 80%. The diagnosis of AMI has remained troublesome due to the non-specific clinical presentation, symptoms and laboratory findings. Early unambiguous diagnosis of AMI is critical to prevent progression from reversible to irreversible transmural intestinal damage, thereby decreasing morbidity and improving survival. The present study aims to validate a panel of plasma biomarkers and investigate volatile organic compound (VOC) profiles in exhaled air as a tool to timely and accurately diagnose AMI.

Methods and analysis: In this international multicentre prospective observational study, 120 patients (>18 years of age) will be recruited with clinical suspicion of AMI. Clinical suspicion is based on: (1) clinical manifestation, (2) physical examination, (3) laboratory measurements and (4) the physician's consideration to perform a CT scan. The patient's characteristics, repetitive blood samples and exhaled air will be prospectively collected. Plasma levels of mucosal damage markers intestinal fatty acid-binding protein and villin-1, as well as transmural damage marker smooth muscle protein 22-alpha, will be assessed by ELISA. Analysis of VOCs in exhaled air will be performed by gas chromatography time-of-flight mass spectrometry. Diagnosis of AMI will be based on CT, endovascular and surgical reports, clinical findings, and (if applicable) verified by histopathological examination.
Ethics and dissemination: The study protocol was approved by the Medical Research Ethics Committee (METC) of Maastricht University Medical Centre+ and Maastricht University (METC azM/UM), the Netherlands (METC19-010) and the Ethics Committee Research UZ/KU Leuven, Belgium (S63500). Executive boards and local METCs of other Dutch participating centres Gelre Ziekenhuizen (Apeldoorn), Medisch Spectrum Twente (Enschede), and University Medical Centre Groningen have granted permission to carry out this study. Study results will be disseminated via open-access peer-reviewed scientific journals and national/international conferences.

Gepubliceerd: BMJ Open. 2023;13(8):e072875.
Impact factor: 2.9 ; Q2

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3. Gamma-Glutamyl Transferase: A Friend against Cholestatic Itch? A Retrospective Observational Data Analysis in Patients with Extrahepatic Cholestasis
Haijer FW, Van Vliet CB, Brusse-Keizer MGJ, Van der Palen JAM, Kerbert-Dreteler MJ, Kolkman JJ.

Methods: We included 235 patients with chronic extrahepatic cholestasis due to pancreatic cancer, cholangiocarcinoma, or papillary carcinoma.
Results: GGT was significantly higher in patients without pruritus (median 967, IQR 587-1571) compared to patients with pruritus (median 561 IQR 266-1084 IU/l) ($p < 0.01$). In contrast, median alkaline phosphatase (AP) was 491 U/L (IQR; 353-684) in patients with pruritus and was not significantly different from 518 U/L (IQR; 353-726) in patients without pruritus ($p = 0.524$). Direct bilirubin was significantly higher in patients with pruritus compared to patients without pruritus (168 μmol/L (IQR; 95-256) vs. 120 μmol/L (IQR; 56.75-185.5)) ($p < 0.01$). After correcting for the extent of cholestasis *via* direct bilirubin, the negative association between GGT and pruritus remained significant and became stronger ($p < 0.001$).
Conclusion: Serum GGT activity is inversely associated with the presence of cholestatic itch in patients with chronic extrahepatic cholestasis.

Gepubliceerd: Int J Hepatol. 2023;2023:2903171.
Impact factor: 1.8 ; Q3

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4. Patient selection for urgent endoscopic retrograde cholangio-pancreatography by endoscopic ultrasound in predicted severe acute biliary pancreatitis (APEC-2): a multicentre prospective study
Hallensleben ND, Stassen PMC, Schepers NJ, Besselink MG, Anten MGF, Bakker OJ, Bollen TL, da Costa DW, van Dijk SM, van Dullemen HM, Dijkgraaf MGW, van Eijck B, van Eijck CHJ, Erkelens W, Erler NS, Fockens P, van Geenen EM, van Grinsven J, Hazen WL, Hollemans RA, van Hooft JE, Jansen JM, Kubben F, Kuiken SD, Poen AC, Quispel R, de Ridder RJ, Römkens TEH, Schoon EJ, Schwartz MP, Seerden TCJ, Smeets X, Spanier BWM, Tan A, Thijs WJ, Timmer R, Umans DS, Venneman NG, Verdonk

RC, Vleggaar FP, van de Vrie W, van Wanrooij RLJ, Witteman BJ, van Santvoort HC, Bouwense SAW, Bruno MJ.

Objective: Routine urgent endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic biliary sphincterotomy (ES) does not improve outcome in patients with predicted severe acute biliary pancreatitis. Improved patient selection for ERCP by means of endoscopic ultrasonography (EUS) for stone/sludge detection may challenge these findings.
Design: A multicentre, prospective cohort study included patients with predicted severe acute biliary pancreatitis without cholangitis. Patients underwent urgent EUS, followed by ERCP with ES in case of common bile duct stones/sludge, within 24 hours after hospital presentation and within 72 hours after symptom onset. The primary endpoint was a composite of major complications or mortality within 6 months after inclusion. The historical control group was the conservative treatment arm (n=113) of the randomised APEC trial (Acute biliary Pancreatitis: urgent ERCP with sphincterotomy versus conservative treatment, patient inclusion 2013-2017) applying the same study design.
Results: Overall, 83 patients underwent urgent EUS at a median of 21 hours (IQR 17-23) after hospital presentation and at a median of 29 hours (IQR 23-41) after start of symptoms. Gallstones/sludge in the bile ducts were detected by EUS in 48/83 patients (58%), all of whom underwent immediate ERCP with ES. The primary endpoint occurred in 34/83 patients (41%) in the urgent EUS-guided ERCP group. This was not different from the 44% rate (50/113 patients) in the historical conservative treatment group (risk ratio (RR) 0.93, 95% CI 0.67 to 1.29; p=0.65). Sensitivity analysis to correct for baseline differences using a logistic regression model also showed no significant beneficial effect of the intervention on the primary outcome (adjusted OR 1.03, 95% CI 0.56 to 1.90, p=0.92).
Conclusion: In patients with predicted severe acute biliary pancreatitis without cholangitis, urgent EUS-guided ERCP with ES did not reduce the composite endpoint of major complications or mortality, as compared with conservative treatment in a historical control group.

Gepubliceerd: Gut. 2023;72(8):1534-42.
Impact factor: 24.5 ; Q1

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5. Endoscopic ultrasonography-guided gastroenterostomy versus surgical gastrojejunostomy for palliation of malignant gastric outlet obstruction (ENDURO): study protocol for a randomized controlled trial

Kastelijn JB, van de Pavert YL, Besselink MG, Fockens P, Voermans RP, van Wanrooij RLJ, de Wijkerslooth TR, Curvers WL, de Hingh I, Bruno MJ, Koerkamp BG, Patijn GA, Poen AC, van Hooft JE, Inderson A, Mieog JSD, Poley JW, Bijlsma A, Lips DJ, Venneman NG, Verdonk RC, van Dullemen HM, Hoogwater FJH, Frederix GWJ, Molenaar IQ, Welsing PMJ, Moons LMG, van Santvoort HC, Vleggaar FP.

Background: Malignant gastric outlet obstruction (GOO) is a debilitating condition that frequently occurs in patients with malignancies of the distal stomach and (peri)ampullary region. The standard palliative treatment for patients with a reasonable life expectancy and adequate performance status is a laparoscopic surgical gastrojejunostomy (SGJ). Recently, endoscopic ultrasound-guided gastroenterostomy (EUS-GE) emerged as a promising alternative to the surgical approach. The present study aims to compare these treatment modalities in terms of efficacy, safety, and costs.
Methods: The ENDURO-study is a multicentre, open-label, parallel-group randomized controlled trial. In total, ninety-six patients with gastric outlet obstruction caused by an irresectable or metastasized malignancy will be 1:1 randomized to either SGJ or EUS-GE. The primary endpoint is time to tolerate at least soft solids. The co-primary endpoint is the proportion of patients with persisting or recurring symptoms of gastric outlet obstruction for which a reintervention is required. Secondary endpoints are technical and clinical success, quality of life, gastroenterostomy dysfunction, reinterventions, time

to reintervention, adverse events, quality of life, time to start chemotherapy, length of hospital stay, readmissions, weight, survival, and costs.
Discussion: The ENDURO-study assesses whether EUS-GE, as compared to SGJ, results in a faster resumption of solid oral intake and is non-inferior regarding reinterventions for persistent or recurrent obstructive symptoms in patients with malignant GOO. This trial aims to guide future treatment strategies and to improve quality of life in a palliative setting.
Trial registration: International Clinical Trials Registry Platform (ICTRP): NL9592. Registered on 07 July 2021.

Gepubliceerd: Trials. 2023;24(1):608.
Impact factor: 2.5 ; Q3

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6. Diagnostic accuracy of endoscopic ultrasonography-guided tissue acquisition prior to resection of pancreatic carcinoma: a nationwide analysis
Quispel R, Schutz HM, Keultjes AWP, Erler NS, Janssen QP, van Hooft JE, Venneman NG, Honkoop P, Hol L, Scheffer RC, Bisseling TM, Voermans RP, Vleggaar FP, Schwartz MP, Verdonk RC, Hoge CV, Kuiken SD, Curvers WL, van Vilsteren FGI, Poen AC, Spanier MB, Bruggink AH, Smedts FM, van Velthuysen MF, van Eijck CH, Besselink MG, Veldt BJ, Koerkamp BG, van Driel L, Bruno MJ.

Introduction: Endoscopic ultrasonography guided tissue acquisition (EUS + TA) is used to provide a tissue diagnosis in patients with suspected pancreatic cancer. Key performance indicators (KPI) for these procedures are rate of adequate sample (RAS) and sensitivity for malignancy (SFM).
Aim: assess practice variation regarding KPI of EUS + TA prior to resection of pancreatic carcinoma in the Netherlands.
Patients and methods: Results of all EUS + TA prior to resection of pancreatic carcinoma from 2014-2018, were extracted from the national Dutch Pathology Registry (PALGA). Pathology reports were classified as: insufficient for analysis (b1), benign (b2), atypia (b3), neoplastic other (b4), suspected malignant (b5), and malignant (b6). RAS was defined as the proportion of EUS procedures yielding specimen sufficient for analysis. SFM was calculated using a strict definition (malignant only, SFM-b6), and a broader definition (SFM-b5+6).
Results: 691 out of 1638 resected patients (42%) underwent preoperative EUS + TA. RAS was 95% (range 89-100%), SFM-b6 was 44% (20-77%), and SFM-b5+6 was 65% (53-90%). All centers met the performance target RAS>85%. Only 9 out of 17 met the performance target SFM-b5+6 > 85%.
Conclusion: This nationwide study detected significant practice variation regarding KPI of EUS + TA procedures prior to surgical resection of pancreatic carcinoma. Therefore, quality improvement of EUS + TA is indicated.

Gepubliceerd: HPB (Oxford). 2023;25(11):1438-45.
Impact factor: 2.9 ; Q2

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7. Suspected common bile duct stones: reduction of unnecessary ERCP by pre-procedural imaging and timing of ERCP
Sperna Weiland CJ, Verschoor EC, Poen AC, Smeets X, Venneman NG, Bhalla A, Witteman BJM, Timmerhuis HC, Umans DS, van Hooft JE, Bruno MJ, Fockens P, Verdonk RC, Drenth JPH, van Geenen EJM.

Background: Endoscopic retrograde cholangiopancreatography (ERCP) is the procedure of choice to remove sludge/stones from the common bile duct (CBD). In a small but clinically important proportion of patients with suspected choledocholithiasis ERCP is negative. This is undesirable

because of ERCP associated morbidity. We aimed to map the diagnostic pathway leading up to ERCP and evaluate ERCP outcome.
Methods: We established a prospective multicenter cohort of patients with suspected CBD stones. We assessed the determinants that were associated with CBD sludge or stone detection upon ERCP.
Results: We established a cohort of 707 patients with suspected CBD sludge or stones (62% female, median age 59 years). ERCP was negative for CBD sludge or stones in 155 patients (22%). Patients with positive ERCPs frequently had pre-procedural endoscopic ultrasonography (EUS) or magnetic resonance cholangiopancreatography (MRCP) imaging (44% vs. 35%; P = 0.045). The likelihood of ERCP sludge and stones detection was higher when the time interval between EUS or MRCP and ERCP was less than 2 days (odds ratio 2.35; 95% CI 1.25-4.44; P = 0.008; number needed to harm 7.7).
Conclusions: Even in the current era of society guidelines and use of advanced imaging CBD sludge or stones are absent in one out of five ERCPs performed for suspected CBD stones. The proportion of unnecessary ERCPs is lower in case of pre-procedural EUS or MRCP. A shorter time interval between EUS or MRCP increases the yield of ERCP for suspected CBD stones and should, therefore, preferably be performed within 2 days before ERCP.

Gepubliceerd: Surg Endosc. 2023;37(2):1194-202.
Impact factor: 3.1 ; Q1

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8. A mixed-methods study to define Textbook Outcome for the treatment of patients with uncomplicated symptomatic gallstone disease with hospital variation analyses in Dutch trial data
Thunnissen FM, Comes DJ, Latenstein CSS, Stommel MWJ, van Laarhoven C, Drenth JPH, Lantinga MA, Atsma F, de Reuver PR, Invited International Collaborators: Venneman NG.

Background: International consensus on the ideal outcome for treatment of uncomplicated symptomatic gallstone disease is absent. This mixed-method study defined a Textbook Outcome (TO) for this large group of patients.
Methods: First, expert meetings were organised with stakeholders to design the survey and identify possible outcomes. To reach consensus, results from expert meetings were converted in a survey for clinicians and for patients. During the final expert meeting, clinicians and patients discussed survey outcomes and a definitive TO was formulated. Subsequently, TO-rate and hospital variation were analysed in Dutch hospital data from patients with uncomplicated gallstone disease.
Results: First expert meetings returned 32 outcomes. Outcomes were distributed in a survey among 830 clinicians from 81 countries and 645 Dutch patients. Consensus-based TO was defined as no more biliary colic, no biliary and surgical complications, and the absence or reduction of abdominal pain. Analysis of individual patient data showed that TO was achieved in 64.2% (1002/1561). Adjusted-TO rates showed modest variation between hospitals (56.6-74.9%).
Conclusion: TO for treatment of uncomplicated gallstone disease was defined as no more biliary colic, no biliary and surgical complications, and absence or reduction of abdominal pain.TO may optimise consistent outcome reporting in care and guidelines for treating uncomplicated gallstone disease.

Gepubliceerd: HPB (Oxford). 2023;25(9):1000-10.
Impact factor: 2.9 ; Q2

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9. Overuse and Misuse of Antibiotics and the Clinical Consequence in Necrotizing Pancreatitis: An Observational Multicenter Study
Timmerhuis HC, van den Berg FF, Noorda PC, van Dijk SM, van Grinsven J, Sperna Weiland CJ, Umans DS, Mohamed YA, Curvers WL, Bouwense SAW, Hadithi M, Inderson A, Issa Y, Jansen JM, de Jonge PJF,

Quispel R, Schwartz MP, Stommel MWJ, Tan A, Venneman NG, Besselink MG, Bruno MJ, Bollen TL, Sieswerda E, Verdonk RC, Voermans RP, van Santvoort HC.

Objective: The use and impact of antibiotics and the impact of causative pathogens on clinical outcomes in a large real-world cohort covering the entire clinical spectrum of necrotizing pancreatitis remain unknown.
Summary background data: International guidelines recommend broad-spectrum antibiotics in patients with suspected infected necrotizing pancreatitis. This recommendation is not based on high-level evidence and clinical effects are unknown.
Materials and methods: This study is a post-hoc analysis of a nationwide prospective cohort of 401 patients with necrotizing pancreatitis in 15 Dutch centers (2010-2019). Across the patient population from the time of admission to 6 months postadmission, multivariable regression analyses were used to analyze (1) microbiological cultures and (2) antibiotic use.
Results: Antibiotics were started in 321/401 patients (80%) administered at a median of 5 days (P25-P75: 1-13) after admission. The median duration of antibiotics was 27 days (P25-P75: 15-48). In 221/321 patients (69%) infection was not proven by cultures at the time of initiation of antibiotics. Empirical antibiotics for infected necrosis provided insufficient coverage in 64/128 patients (50%) with a pancreatic culture. Prolonged antibiotic therapy was associated with Enterococcus infection (OR 1.08 [95% CI 1.03-1.16], P =0.01). Enterococcus infection was associated with new/persistent organ failure (OR 3.08 [95% CI 1.35-7.29], P <0.01) and mortality (OR 5.78 [95% CI 1.46-38.73], P =0.03). Yeast was found in 30/147 cultures (20%).
Discussion: In this nationwide study of patients with necrotizing pancreatitis, the vast majority received antibiotics, typically administered early in the disease course and without a proven infection. Empirical antibiotics were inappropriate based on pancreatic cultures in half the patients. Future clinical research and practice must consider antibiotic selective pressure due to prolonged therapy and coverage of Enterococcus and yeast. Improved guidelines on antimicrobial diagnostics and therapy could reduce inappropriate antibiotic use and improve clinical outcomes.

Gepubliceerd: Ann Surg. 2023;278(4):e812-e9.
Impact factor: 10.1; Q1

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10. Short-term and Long-term Outcomes of a Disruption and Disconnection of the Pancreatic Duct in Necrotizing Pancreatitis: A Multicenter Cohort Study in 896 Patients

Timmerhuis HC, van Dijk SM, Hollemans RA, Sperna Weiland CJ, Umans DS, Boxhoorn L, Hallensleben NH, van der Sluijs R, Brouwer L, van Duijvendijk P, Kager L, Kuiken S, Poley JW, de Ridder R, Römkens TEH, Quispel R, Schwartz MP, Tan A, Venneman NG, Vleggaar FP, van Wanrooij RLJ, Witteman BJ, van Geenen EJ, Molenaar IQ, Bruno MJ, van Hooft JE, Besselink MG, Voermans RP, Bollen TL, Verdonk RC, van Santvoort HC.

Introduction: Necrotizing pancreatitis may result in a disrupted or disconnected pancreatic duct (DPD) with the potential for long-lasting negative impact on a patient's clinical outcome. There is a lack of detailed data on the full clinical spectrum of DPD, which is critical for the development of better diagnostic and treatment strategies.
Methods: We performed a long-term post hoc analysis of a prospectively collected nationwide cohort of 896 patients with necrotizing pancreatitis (2005-2015). The median follow-up after hospital admission was 75 months (P25-P75: 41-151). Clinical outcomes of patients with and without DPD were compared using regression analyses, adjusted for potential confounders. Predictive features for DPD were explored.
Results: DPD was confirmed in 243 (27%) of the 896 patients and resulted in worse clinical outcomes during both the patient's initial admission and follow-up. During hospital admission, DPD was associated with an increased rate of new-onset intensive care unit admission (adjusted odds ratio

[aOR] 2.52; 95% confidence interval [CI] 1.62-3.93), new-onset organ failure (aOR 2.26; 95% CI 1.45-3.55), infected necrosis (aOR 4.63; 95% CI 2.87-7.64), and pancreatic interventions (aOR 7.55; 95% CI 4.23-13.96). During long-term follow-up, DPD increased the risk of pancreatic intervention (aOR 9.71; 95% CI 5.37-18.30), recurrent pancreatitis (aOR 2.08; 95% CI 1.32-3.29), chronic pancreatitis (aOR 2.73; 95% CI 1.47-5.15), and endocrine pancreatic insufficiency (aOR 1.63; 95% CI 1.05-2.53). Central or subtotal pancreatic necrosis on computed tomography (OR 9.49; 95% CI 6.31-14.29) and a high level of serum C-reactive protein in the first 48 hours after admission (per 10-point increase, OR 1.02; 95% CI 1.00-1.03) were identified as independent predictors for developing DPD.
Discussion: At least 1 of every 4 patients with necrotizing pancreatitis experience DPD, which is associated with detrimental, short-term and long-term interventions, and complications. Central and subtotal pancreatic necrosis and high levels of serum C-reactive protein in the first 48 hours are independent predictors for DPD.

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Impact factor: 10.2 ; Q1

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11. Prospective multicentre study of indications for surgery in patients with idiopathic acute pancreatitis following endoscopic ultrasonography (PICUS)
Umans DS, Timmerhuis HC, Anten MGF, Bhalla A, Bijlsma RA, Boxhoorn L, Brink MA, Bruno MJ, Curvers WL, van Eijck BC, Erkelens GW, van Geenen EJM, Hazen WL, Hoge CV, Hol L, Inderson A, Kager LM, Kuiken SD, Perk LE, Quispel R, Römkens TEH, Sperna Weiland CJ, Thijssen AY, Venneman NG, Verdonk RC, van Wanrooij RLJ, Witteman BJ, Besselink MG, van Hooft JE.

Background: Cholecystectomy in patients with idiopathic acute pancreatitis (IAP) is controversial. A randomized trial found cholecystectomy to reduce the recurrence rate of IAP but did not include preoperative endoscopic ultrasonography (EUS). As EUS is effective in detecting gallstone disease, cholecystectomy may be indicated only in patients with gallstone disease. This study aimed to determine the diagnostic value of EUS in patients with IAP, and the rate of recurrent pancreatitis in patients in whom EUS could not determine the aetiology (EUS-negative IAP).
Methods: This prospective multicentre cohort study included patients with a first episode of IAP who underwent outpatient EUS. The primary outcome was detection of aetiology by EUS. Secondary outcomes included adverse events after EUS, recurrence of pancreatitis, and quality of life during 1-year follow-up.
Results: After screening 957 consecutive patients with acute pancreatitis from 24 centres, 105 patients with IAP were included and underwent EUS. In 34 patients (32 per cent), EUS detected an aetiology: (micro)lithiasis and biliary sludge (23.8 per cent), chronic pancreatitis (6.7 per cent), and neoplasms (2.9 per cent); 2 of the latter patients underwent pancreatoduodenectomy. During 1-year follow-up, the pancreatitis recurrence rate was 17 per cent (12 of 71) among patients with EUS-negative IAP versus 6 per cent (2 of 34) among those with positive EUS. Recurrent pancreatitis was associated with poorer quality of life.
Conclusion: EUS detected an aetiology in a one-third of patients with a first episode of IAP, requiring mostly cholecystectomy or pancreatoduodenectomy. The role of cholecystectomy in patients with EUS-negative IAP remains uncertain and warrants further study.

Gepubliceerd: Br J Surg. 2023;110(12):1877-82.
Impact factor: 9.6 ; Q1

Totale impact factor: 94.6
Gemiddelde impact factor: 8.6

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 1.8
Gemiddelde impact factor: 1.8

Medical School Twente

1. Advancing Digital Solutions to Overcome Longstanding Barriers in Asthma and COPD Management
Bosnic-Anticevich S, Bakerly ND, Chrystyn H, Hew M, van der Palen J.

Maintenance therapy delivered via inhaler is central to asthma and chronic obstructive pulmonary disease (COPD) management. Poor adherence to inhaled medication and errors in inhalation technique have long represented major barriers to the optimal management of these chronic conditions. Technological innovations may provide a means of overcoming these barriers. This narrative review examines ongoing advances in digital technologies relevant to asthma and COPD with the potential to inform clinical decision-making and improve patient care. Digital inhaler devices linked to mobile apps can help bring about changes in patients' behaviors and attitudes towards disease management, particularly when they build in elements of interactivity and gamification. They can also support ongoing technique education, empowering patients and helping providers maximize the value of consultations and develop effective action plans informed by insights into the patient's inhaler use patterns and their respiratory health. When combined with innovative techniques such as machine learning, digital devices have the potential to predict exacerbations and prompt pre-emptive intervention. Finally, digital devices may support an advanced precision medicine approach to respiratory disease management and help support shared decision-making. Further work is needed to increase uptake of digital devices and integrate their use into care pathways before their full potential in personalized asthma and COPD management can be realized.

Gepubliceerd: Patient Prefer Adherence. 2023;17:259-72.
Impact factor: 2.2 ; Q3

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2. Implementation of Recommendations on the Use of Corticosteroids in Severe COVID-19
Camirand-Lemyre F, Merson L, Tirupakuzhi Vijayaraghavan BK, Burrell AJC, Citarella BW, Domingue MP, Lévesque S, Usuf E, Wils EJ, Ohshimo S, Martin-Loeches I, Sandulescu O, Laake JH, Lamontagne F, ISARIC Clinical Characterisation 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.

Importance: Research diversity and representativeness are paramount in building trust, generating valid biomedical knowledge, and possibly in implementing clinical guidelines.
Objectives: To compare variations over time and across World Health Organization (WHO) geographic regions of corticosteroid use for treatment of severe COVID-19; secondary objectives were to evaluate the association between the timing of publication of the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial (June 2020) and the WHO guidelines for corticosteroids (September 2020) and the temporal trends observed in corticosteroid use by region and to describe the geographic distribution of the recruitment in clinical trials that informed the WHO recommendation.
Design, setting, and participants: This prospective cohort study of 434 851 patients was conducted between January 31, 2020, and September 2, 2022, in 63 countries worldwide. The data were collected under the auspices of the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC)-WHO Clinical Characterisation Protocol for Severe Emerging Infections. Analyses were restricted to patients hospitalized for severe COVID-19 (a subset of the ISARIC data set).
Exposure: Corticosteroid use as reported to the ISARIC-WHO Clinical Characterisation Protocol for Severe Emerging Infections.
Main outcomes and measures: Number and percentage of patients hospitalized with severe COVID-19 who received corticosteroids by time period and by WHO geographic region.

Results: Among 434 851 patients with confirmed severe or critical COVID-19 for whom receipt of corticosteroids could be ascertained (median [IQR] age, 61.0 [48.0-74.0] years; 53.0% male), 174 307 (40.1%) received corticosteroids during the study period. Of the participants in clinical trials that informed the guideline, 91.6% were recruited from the United Kingdom. In all regions, corticosteroid use for severe COVID-19 increased, but this increase corresponded to the timing of the RECOVERY trial (time-interruption coefficient 1.0 [95% CI, 0.9-1.2]) and WHO guideline (time-interruption coefficient 1.9 [95% CI, 1.7-2.0]) publications only in Europe. At the end of the study period, corticosteroid use for treatment of severe COVID-19 was highest in the Americas (5421 of 6095 [88.9%]; 95% CI, 87.7-90.2) and lowest in Africa (31 588 of 185 191 [17.1%]; 95% CI, 16.8-17.3).
Conclusions and relevance: The results of this cohort study showed that implementation of the guidelines for use of corticosteroids in the treatment of severe COVID-19 varied geographically. Uptake of corticosteroid treatment was lower in regions with limited clinical trial involvement. Improving research diversity and representativeness may facilitate timely knowledge uptake and guideline implementation.

Gepubliceerd: JAMA Netw Open. 2023;6(12):e2346502.
Impact factor: 13.8 ; Q1

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3. Neurological manifestations of COVID-19 in adults and children
Cho SM, White N, Premraj L, Battaglini D, Fanning J, Suen J, Bassi GL, Fraser J, Robba C, Griffee M, Singh B, Citarella BW, Merson L, Solomon T, Thomson D, ISARIC Clinical Characterisation 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.

Different neurological manifestations of coronavirus disease 2019 (COVID-19) in adults and children and their impact have not been well characterized. We aimed to determine the prevalence of neurological manifestations and in-hospital complications among hospitalized COVID-19 patients and ascertain differences between adults and children. We conducted a prospective multicentre observational study using the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) cohort across 1507 sites worldwide from 30 January 2020 to 25 May 2021. Analyses of neurological manifestations and neurological complications considered unadjusted prevalence estimates for predefined patient subgroups, and adjusted estimates as a function of patient age and time of hospitalization using generalized linear models. Overall, 161 239 patients (158 267 adults; 2972 children) hospitalized with COVID-19 and assessed for neurological manifestations and complications were included. In adults and children, the most frequent neurological manifestations at admission were fatigue (adults: 37.4%; children: 20.4%), altered consciousness (20.9%; 6.8%), myalgia (16.9%; 7.6%), dysgeusia (7.4%; 1.9%), anosmia (6.0%; 2.2%) and seizure (1.1%; 5.2%). In adults, the most frequent in-hospital neurological complications were stroke (1.5%), seizure (1%) and CNS infection (0.2%). Each occurred more frequently in intensive care unit (ICU) than in non-ICU patients. In children, seizure was the only neurological complication to occur more frequently in ICU versus non-ICU (7.1% versus 2.3%, $P < 0.001$). Stroke prevalence increased with increasing age, while CNS infection and seizure steadily decreased with age. There was a dramatic decrease in stroke over time during the pandemic. Hypertension, chronic neurological disease and the use of extracorporeal membrane oxygenation were associated with increased risk of stroke. Altered consciousness was associated with CNS infection, seizure and stroke. All in-hospital neurological complications were associated with increased odds of death. The likelihood of death rose with increasing age, especially after 25 years of age. In conclusion, adults and children have different neurological manifestations and in-hospital complications associated with COVID-19. Stroke risk increased with increasing age, while CNS infection and seizure risk decreased with age.

Gepubliceerd: Brain. 2023;146(4):1648-61.

Impact factor: 14.5 ; Q1

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4. Evaluation of Exacerbation and Symptom-Free Time in Patients with COPD
de Vries MI, Effing TW, van der Palen J, Schrijver J, van der Valk P, Lenferink A.

In clinical practice, clinicians mainly focus on Chronic Obstructive Pulmonary Disease (COPD) exacerbations and symptoms, while patients may prefer to evaluate periods free of COPD exacerbations and deteriorated symptoms. The latter would suit the positive health approach that centralizes people and their beliefs. We aimed to identify patient characteristics and health outcomes relating to: 1) COPD exacerbation-free days; 2) days with no more symptoms than usual; and 3) combined COPD exacerbation and comorbid flare-up-free days (i.e. chronic heart failure, anxiety, depression flare-ups) using negative binomial regression analyzes. Data were obtained from two self-management intervention trials including COPD patients with and without comorbidities. 313 patients (mean age 66.0 years, 63.6% male, 68.7% comorbidity) were included. Better baseline chronic respiratory questionnaire (CRQ) fatigue (incidence rate ratio (IRR) = 1.03 (95% CI 1.01-1.05), p = 0.02) and mastery scores (IRR = 1.03 (95% CI 1.00-1.06), p = 0.04) and fewer courses of antibiotics (IRR = 0.95 (95% CI 0.94-0.96), p < 0.01) were related to more COPD exacerbation-free days. Additionally, better baseline CRQ fatigue (IRR = 1.05 (95% CI 1.00-1.10), p = 0.04) and mastery scores (IRR = 1.06 (95% CI 1.00-1.12), p = 0.04), fewer courses of antibiotics (IRR = 0.94 (95% CI 0.91-0.96), p < 0.01), and improved CRQ dyspnea scores over 12 months of follow-up (IRR = 1.07 (95% CI 1.01-1.12), p < 0.01) were correlated to more days free of deteriorated symptoms. Less baseline dyspnea (modified Medical Research Council score) (IRR = 0.95 (95% CI 0.92-0.98), p < 0.01) and fewer courses of antibiotics (IRR = 0.94 (95% CI 0.93-0.95), p < 0.01) were associated with more combined COPD exacerbation and comorbid flare-up-free days. Healthcare professionals should be aware that less fatigue and better mastering of COPD relate to more exacerbation and symptom-free time in COPD patients.

Gepubliceerd: Copd. 2023;20(1):9-17.
Impact factor: 2.2 ; Q4

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5. An optimized D-dimer cut-off value to predict pulmonary thromboembolism in COVID-19 patients
Engels SYH, van Veen I, Oudkerk M, van der Palen J, Heuvelmans MA.

Pulmonary thromboembolism (PTE) is a common complication in coronavirus disease 2019 (COVID-19) patients. Elevated D-dimer levels are observed even in the absence of PTE, reducing its discriminative ability as a screening test. It is unknown whether conventional D-dimer cut-off values, as used in the YEARS algorithm, apply to COVID-19 patients. This study aimed to determine the optimal D-dimer cut-off value to predict PTE in COVID-19 patients. All confirmed COVID-19 patients with a computed tomography pulmonary angiography (CTPA) performed ≤5 days after admission due to suspicion of PTE between March 2020 and February 2021, at Medisch Spectrum Twente, The Netherlands, were retrospectively analyzed. The association between PTE and D-dimer levels prior to CTPA, and other potential predictors, was analyzed using logistic regression analyses. The optimal cut-off value was identified using receiver operating characteristic (ROC) curve analyses. In 142 patients, PTE prevalence was 20.4%. The optimal cut-off value was 750 ng/mL (sensitivity 100%; specificity 19.5%; negative predictive value 100%; positive predictive value 24.2%). In total, 15 of 113 (13%) patients without PTE had a D-dimer level ≥500 and <750 ng/mL. In our population of patients hospitalized with COVID-19, a D-dimer level <750 ng/mL safely excluded PTE. Compared to the YEARS

500 ng/mL cut-off value, 13% fewer patients are in need of a CTPA, with similar sensitivity. Future research is required for external validation.

Gepubliceerd: J Thorac Dis. 2023;15(11):6317-22.
Impact factor: 2.5 ; Q3

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6. A retrospective analysis of the association of effort-independent cardiopulmonary exercise test variables with postoperative complications in patients who underwent elective colorectal surgery
Franssen RFW, Berkel AEM, Ten Cate DWG, van der Palen J, van Meeteren NLU, Vogelaar FJ, Slooter G, Klaase JM, Janssen-Heijnen MLG, Bongers BC.

Purpose: This study aimed to investigate the association of effort-independent variables derived from the preoperative cardiopulmonary exercise test (CPET) with 30-day postoperative complications after elective colorectal surgery.
Methods: A multicenter (n=4) retrospective explorative study was performed using data of patients who completed a preoperative CPET and underwent elective colorectal surgery. The preoperative slope of the relation between minute ventilation and carbon dioxide production (VE/VCO_2-slope) and the oxygen uptake efficiency slope (OUES), as well as 30-day postoperative complications, were assessed. Multivariable logistic regression analyses and receiver operating characteristic (ROC) curves were used to investigate the prognostic value of the relationship between these preoperative CPET-derived effort-independent variables and postoperative complications.
Results: Data from 102 patients (60.1% males) with a median age of 72.0 (interquartile range 67.8-77.4) years were analyzed. Forty-four patients (43.1%) had one or more postoperative complications (of which 52.3% general and 77.3% surgical complications). Merely 10 (9.8%) patients had a general complication only. In multivariate analysis adjusted for surgical approach (open versus minimally invasive surgery), the VE/VCO_2-slope (odds ratio (OR) 1.08, confidence interval (CI) 1.02-1.16) and OUES (OR 0.94, CI 0.89-1.00) were statistically significant associated with the occurrence of 30-day postoperative complications.
Conclusion: The effort-independent VE/VCO_2-slope and OUES might be used to assist in future preoperative risk assessment and could especially be of added value in patients who are unable or unwilling to deliver a maximal cardiorespiratory effort. Future research should reveal the predictive value of these variables individually and/or in combination with other prognostic (CPET-derived) variables for postoperative complications.
Trial registration number: ClinicalTrials.gov NCT05331196.

Gepubliceerd: Langenbecks Arch Surg. 2023;409(1):7.
Impact factor: 2.3 ; Q2

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7. Thrombotic and hemorrhagic complications of COVID-19 in adults hospitalized in high-income countries compared with those in adults hospitalized in low- and middle-income countries in an international registry
Griffee MJ, Bozza PT, Reyes LF, Eddington DP, Rosenberger D, Merson L, Citarella BW, Fanning JP, Alexander PMA, Fraser J, Dalton H, Cho SM, ISARIC Clinical Characterisation 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: COVID-19 has been associated with a broad range of thromboembolic, ischemic, and hemorrhagic complications (coagulopathy complications). Most studies have focused on patients with severe disease from high-income countries (HICs).

Objectives: The main aims were to compare the frequency of coagulopathy complications in developing countries (low- and middle-income countries [LMICs]) with those in HICs, delineate the frequency across a range of treatment levels, and determine associations with in-hospital mortality.
Methods: Adult patients enrolled in an observational, multinational registry, the International Severe Acute Respiratory and Emerging Infections COVID-19 study, between January 1, 2020, and September 15, 2021, met inclusion criteria, including admission to a hospital for laboratory-confirmed, acute COVID-19 and data on complications and survival. The advanced-treatment cohort received care, such as admission to the intensive care unit, mechanical ventilation, or inotropes or vasopressors; the basic-treatment cohort did not receive any of these interventions.
Results: The study population included 495,682 patients from 52 countries, with 63% from LMICs and 85% in the basic treatment cohort. The frequency of coagulopathy complications was higher in HICs (0.76%-3.4%) than in LMICs (0.09%-1.22%). Complications were more frequent in the advanced-treatment cohort than in the basic-treatment cohort. Coagulopathy complications were associated with increased in-hospital mortality (odds ratio, 1.58; 95% CI, 1.52-1.64). The increased mortality associated with these complications was higher in LMICs (58.5%) than in HICs (35.4%). After controlling for coagulopathy complications, treatment intensity, and multiple other factors, the mortality was higher among patients in LMICs than among patients in HICs (odds ratio, 1.45; 95% CI, 1.39-1.51).
Conclusion: In a large, international registry of patients hospitalized for COVID-19, coagulopathy complications were more frequent in HICs than in LMICs (developing countries). Increased mortality associated with coagulopathy complications was of a greater magnitude among patients in LMICs. Additional research is needed regarding timely diagnosis of and intervention for coagulation derangements associated with COVID-19, particularly for limited-resource settings.

Gepubliceerd: Res Pract Thromb Haemost. 2023;7(5):102142.
Impact factor: 4.6 ; Q2

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8. Gamma-Glutamyl Transferase: A Friend against Cholestatic Itch? A Retrospective Observational Data Analysis in Patients with Extrahepatic Cholestasis
Haijer FW, Van Vliet CB, Brusse-Keizer MGJ, Van der Palen JAM, Kerbert-Dreteler MJ, Kolkman JJ.

Methods: We included 235 patients with chronic extrahepatic cholestasis due to pancreatic cancer, cholangiocarcinoma, or papillary carcinoma.
Results: GGT was significantly higher in patients without pruritus (median 967, IQR 587-1571) compared to patients with pruritus (median 561 IQR 266-1084 IU/l) ($p < 0.01$). In contrast, median alkaline phosphatase (AP) was 491 U/L (IQR; 353-684) in patients with pruritus and was not significantly different from 518 U/L (IQR; 353-726) in patients without pruritus ($p = 0.524$). Direct bilirubin was significantly higher in patients with pruritus compared to patients without pruritus (168 μmol/L (IQR; 95-256) vs. 120 μmol/L (IQR; 56.75-185.5)) ($p < 0.01$). After correcting for the extent of cholestasis *via* direct bilirubin, the negative association between GGT and pruritus remained significant and became stronger ($p < 0.001$).
Conclusion: Serum GGT activity is inversely associated with the presence of cholestatic itch in patients with chronic extrahepatic cholestasis.

Gepubliceerd: Int J Hepatol. 2023;2023:2903171.
Impact factor: 1.8 ; Q3

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9. A mobilization poster stimulates early in-hospital rehabilitation after cardiac surgery: a prospective sequential-group study

Halfwerk FR, Wielens N, Hulskotte S, Brusse-Keizer M, Grandjean JG.

Background: Patients infrequently mobilize at the surgical ward after cardiac surgery. Inactivity results in prolonged hospital stay, readmissions and increased cardiovascular mortality. Next, the course of in-hospital mobilization activities for patients is unclear. The aim was to evaluate early mobilization after heart surgery with a mobilization poster on the Activity Classification Guide for Inpatient Activities score from the American College for Sports Medicine (ACSM). Second, to develop a Thorax Centrum Twente (TCT) score to assess distinctive activities performed.
Methods: A poster was developed for the Moving is Improving! study to stimulate hospital mobilization after heart surgery. In this sequential-group study at a cardiothoracic surgery ward, 32 patients were included in the usual care group and 209 patients in the poster mobilization group. Change of ACSM and TCT scores over time were both defined as primary endpoints. Secondary endpoints included length of stay and survival. A subgroup analysis for coronary artery bypass grafting (CABG) was performed.
Results: ACSM score increased during hospital stay ($p < 0.001$). No significant increase of ACSM score was observed with a mobilization poster ($p = 0.27$), nor in the CABG subgroup ($p = 0.15$). The poster increased mobility to chair, toilet, corridor (all $p < 0.01$) and cycle ergometer ($p = 0.02$) as measured by the activity-specific TCT scores, without differences in length of stay or survival.
Conclusions: ACSM score measured day-to-day functional changes, without significant differences between the poster mobilization and usual care group. Actual activities measured with the TCT score did improve. The mobilization poster is now new standard care, and effects in other centers and other departments should be assessed.
Trial registration: This study does not fall under the ICMJE trial definition and was not registered.

Gepubliceerd: J Cardiothorac Surg. 2023;18(1):83.
Impact factor: 1.6 ; Q3

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10. Functional recovery after reduced pediatric fractures of the forearm with respect to perceived limitations, common post-traumatic symptoms, range of motion, and dexterity: a prospective study
Hepping AM, Barvelink B, Ploegmakers JJW, van der Palen J, Geertzen JHB, Bulstra SK, Harbers JS, Stevens M.

Purpose: Studies on functional recovery after pediatric forearm fractures are scarce. Outcome measures are usually (retrospectively) incorporated to compare treatments. How these parameters recover has only rarely fallen within the scope. Aim was to provide insight into "normal recovery" by evaluating how limitations, post-traumatic symptoms, range of motion (ROM) and dexterity recuperate.
Materials and methods: Prospective observational study regarding children 4 and 18 years with a reduced forearm fracture. Limitations, post-traumatic symptoms, ROM, and dexterity were evaluated 6 weeks, 3 and 6 months post-trauma. ROM of the unaffected side was used as a baseline.
Results: Of 54 participants 25.9% and 5.9% perceived limitations after 3 respectively 6 months. Pain, swelling and hypertrichosis were common symptoms. Movements distal from the elbow were restrained 6 weeks post-trauma. Supination and palmar flexion were most affected, followed by dorsal flexion and pronation. Palmar flexion and pronation were still affected after 3 months and associated with treatment invasiveness. Dexterity was diminished at 6 weeks only.
Conclusions: Mild limitations are common. Further investigation of the association between pain, reduced sensitivity and hypertrichosis with treatment invasiveness is warranted. Regarding ROM supination, pronation, palmar and dorsal flexion should be incorporated in future studies. Dexterity is an unsuitable outcome measure.IMPLICATIONS FOR REHABILITATIONThis study relates to monitoring recovery from pediatric forearm fractures.Physicians ought to realize that one in four children experience limitations preceding 3 months post-trauma, in which case involvement of a hand

therapist should be considered.Pain, swelling and especially hypertrichosis are common post-traumatic symptoms in children and should on itself not immediately raise concerns for complex regional pain syndrome (CRPS).To assess recovery of range of motion measuring pronation, supination, dorsal, and palmar flexion is sufficient.

Gepubliceerd: Disabil Rehabil. 2023;45(21):3560-6.
Impact factor: 2.2 ; Q2

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11. Characteristics and outcomes of an international cohort of 600 000 hospitalized patients with COVID-19

Kartsonaki C, Baillie JK, Barrio NG, Baruch J, Beane A, Blumberg L, Bozza F, Broadley T, Burrell A, Carson G, Citarella BW, Dagens A, Dankwa EA, Donnelly CA, Dunning J, Elotmani L, Escher M, Farshait N, Goffard JC, Gonçalves BP, Hall M, Hashmi M, Sim Lim Heng B, Ho A, Jassat W, Pedrera Jiménez M, Laouenan C, Lissauer S, Martin-Loeches I, Mentré F, Merson L, Morton B, Munblit D, Nekliudov NA, Nichol AD, Singh Oinam BC, Ong D, Panda PK, Petrovic M, Pritchard MG, Ramakrishnan N, Ramos GV, Roger C, Sandulescu O, Semple MG, Sharma P, Sigfrid L, Somers EC, Streinu-Cercel A, Taccone F, Vecham PK, Kumar Tirupakuzhi Vijayaraghavan B, Wei J, Wils EJ, Ci Wong X, Horby P, Rojek A, Olliaro PL, ISARIC Clinical Characterisation 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: We describe demographic features, treatments and clinical outcomes in the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) COVID-19 cohort, one of the world's largest international, standardized data sets concerning hospitalized patients.
Methods: The data set analysed includes COVID-19 patients hospitalized between January 2020 and January 2022 in 52 countries. We investigated how symptoms on admission, co-morbidities, risk factors and treatments varied by age, sex and other characteristics. We used Cox regression models to investigate associations between demographics, symptoms, co-morbidities and other factors with risk of death, admission to an intensive care unit (ICU) and invasive mechanical ventilation (IMV).
Results: Data were available for 689 572 patients with laboratory-confirmed (91.1%) or clinically diagnosed (8.9%) SARS-CoV-2 infection from 52 countries. Age [adjusted hazard ratio per 10 years 1.49 (95% CI 1.48, 1.49)] and male sex [1.23 (1.21, 1.24)] were associated with a higher risk of death. Rates of admission to an ICU and use of IMV increased with age up to age 60 years then dropped. Symptoms, co-morbidities and treatments varied by age and had varied associations with clinical outcomes. The case-fatality ratio varied by country partly due to differences in the clinical characteristics of recruited patients and was on average 21.5%.
Conclusions: Age was the strongest determinant of risk of death, with a ∼30-fold difference between the oldest and youngest groups; each of the co-morbidities included was associated with up to an almost 2-fold increase in risk. Smoking and obesity were also associated with a higher risk of death. The size of our international database and the standardized data collection method make this study a comprehensive international description of COVID-19 clinical features. Our findings may inform strategies that involve prioritization of patients hospitalized with COVID-19 who have a higher risk of death.

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Impact factor: 7.7 ; Q1

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12. 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. 2023;37:103292.
Impact factor: 4.2 ; Q2

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13. Diagnosing Non-Small Cell Lung Cancer by Exhaled Breath Profiling Using an Electronic Nose: A Multicenter Validation Study
Kort S, Brusse-Keizer M, Schouwink H, Citgez E, de Jongh FH, van Putten JWG, van den Borne B, Kastelijn EA, Stolz D, Schuurbiers M, van den Heuvel MM, van Geffen WH, van der Palen J.

Background: Despite the potential of exhaled breath analysis of volatile organic compounds to diagnose lung cancer, clinical implementation has not been realized, partly due to the lack of validation studies.
Research question: This study addressed two questions. First, can we simultaneously train and validate a prediction model to distinguish patients with non-small cell lung cancer from non-lung

cancer subjects based on exhaled breath patterns? Second, does addition of clinical variables to exhaled breath data improve the diagnosis of lung cancer?
Study design and methods: In this multicenter study, subjects with non-small cell lung cancer and control subjects performed 5 min of tidal breathing through the aeoNose, a handheld electronic nose device. A training cohort was used for developing a prediction model based on breath data, and a blinded cohort was used for validation. Multivariable logistic regression analysis was performed, including breath data and clinical variables, in which the formula and cutoff value for the probability of lung cancer were applied to the validation data.
Results: A total of 376 subjects formed the training set, and 199 subjects formed the validation set. The full training model (including exhaled breath data and clinical parameters from the training set) were combined in a multivariable logistic regression analysis, maintaining a cut off of 16% probability of lung cancer, resulting in a sensitivity of 95%, a specificity of 51%, and a negative predictive value of 94%; the area under the receiver-operating characteristic curve was 0.87. Performance of the prediction model on the validation cohort showed corresponding results with a sensitivity of 95%, a specificity of 49%, a negative predictive value of 94%, and an area under the receiver-operating characteristic curve of 0.86.
Interpretation: Combining exhaled breath data and clinical variables in a multicenter, multi-device validation study can adequately distinguish patients with lung cancer from subjects without lung cancer in a noninvasive manner. This study paves the way to implement exhaled breath analysis in the daily practice of diagnosing lung cancer.
Clinical trial registration: The Netherlands Trial Register; No.: NL7025; URL: https://trialregister.nl/trial/7025.

Gepubliceerd: Chest. 2023;163(3):697-706.
Impact factor: 10.1 ; Q1

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14. Augmenting outpatient alcohol treatment as usual with online approach bias modification training: A double-blind randomized controlled trial
Laurens MC, Postel MG, Brusse-Keizer M, Pieterse ME, Ben Allouch S, Bohlmeijer ET, Salemink E.

Previous research shows that automatic tendency to approach alcohol plays a causal role in problematic alcohol use and can be retrained by Approach Bias Modification (ApBM). ApBM has been shown to be effective for patients diagnosed with alcohol use disorder (AUD) in inpatient treatment. This study aimed to investigate the effectiveness of adding an online ApBM to treatment as usual (TAU) in an outpatient setting compared to receiving TAU with an online placebo training. 139 AUD patients receiving face-to-face or online treatment as usual (TAU) participated in the study. The patients were randomized to an active or placebo version of 8 sessions of online ApBM over a 5-week period. The weekly consumed standard units of alcohol (primary outcome) was measured at pre-and post-training, 3 and 6 months follow-up. Approach tendency was measured pre-and-post ApBM training. No additional effect of ApBM was found on alcohol intake, nor other outcomes such as craving, depression, anxiety, or stress. A significant reduction of the alcohol approach bias was found. This research showed that approach bias retraining in AUD patients in an outpatient treatment setting reduces the tendency to approach alcohol, but this training effect does not translate into a significant difference in alcohol reduction between groups. Explanations for the lack of effects of ApBM on alcohol consumption are treatment goal and severity of AUD. Future ApBM research should target outpatients with an abstinence goal and offer alternative, more user-friendly modes of delivering ApBM training.

Gepubliceerd: Addict Behav. 2023;142:107630.
Impact factor: 4.4 ; Q1

15. Cost-utility analysis of a structured medication review compared to usual care in Parkinson's disease
Oonk NGM, Dorresteijn LDA, van den Berg AD, van der Palen J, Movig KLL, Nijmeijer HW, van Kesteren ME, Koffijberg H.

Purpose: For controlling symptoms in Parkinson's disease (PD) together with treating additional comorbidities, patients often face complex medication regimens, with suboptimal adherence, drug-related problems, and diminished therapy efficacy as a common consequence. A medication review could potentially tackle these issues, among others by optimizing drug treatment. Even if no change in clinical outcomes is observed, this intervention might decrease health care costs by reducing drug-related problems and hospital admissions. This study aimed to gain more insight in the health benefits and costs of a structured medication review (SMR) in PD.
Methods: A cost-utility analysis was performed, based on a multicenter randomized controlled trial with 202 PD patients with polypharmacy. The intervention group received an SMR, whereas the control group received usual care. The intervention effect after 6 months of follow-up was presented as incremental quality-adjusted life years (QALY) using the EQ-5D-5L questionnaire. Costs were based on real-world data. Missing data was imputed using multiple imputation techniques. Bootstrapping was used to estimate the uncertainty in all health and economic outcomes.
Results: The QALY gain in the intervention group compared to the control group was - 0.011 (95% CI - 0.043; 0.020). Incremental costs were €433 (95% CI - 873; 1687). When adapting a willingness-to-pay threshold of €20,000/QALY and €80,000/QALY, the probability of SMRs being cost-effective was 18% and 30%, respectively.
Conclusion: A community pharmacist-led SMR in PD patients in the current setting shows no apparent benefit and is not cost-effective after 6 months, compared to usual care.
Trial registration: Netherlands Trial Register, NL4360. Registered 17 March 2014.

Gepubliceerd: Eur J Clin Pharmacol. 2023;79(2):289-97.
Impact factor: 2.9 ; Q3

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16. Facilitators and Barriers of Adherence to Multi-Disease Exacerbation Action Plans in COPD Patients - A Qualitative Study
Schrijver J, Effing T, Brusse-Keizer M, van der Palen J, van der Valk P, Lenferink A.

Whereas exacerbation action plans to self-manage Chronic Obstructive Pulmonary Disease (COPD) significantly improve health outcomes, patients' adherence to those action plans is often poor. This study aimed to identify facilitators and barriers of adherence to tailored multi-disease exacerbation action plans. We also explored patients' perspectives toward disease management roles. Individual semi-structured interviews were conducted with a sample of COPD patients who completed a Dutch-Australian self-management intervention evaluating tailored exacerbation action plans for COPD and relevant comorbidities. Interviews were thematically analyzed using a deductive approach guided by the Capability, Opportunity and Motivation of Behavior (COM-B) model. In 2016, ten patients (5 Australian; 5 Dutch; 6 men; age 59-83 years) were interviewed at the end of their one-year follow-up. Facilitators of adherence included improved patients' comprehension of disease and treatment, positive feelings about the intervention, improved self-confidence, and professional support. Barriers included difficulties to recognize symptoms, dislike toward daily symptom monitoring, negative feelings about the intervention, negative mood state, and complexity of symptom diaries and action plans. Patients indicated three distinctive perspectives of their own and their healthcare professional's role in their disease management: 1) patients felt mainly responsible; 2) patients felt

shared responsibility with their healthcare professional; and 3) patients felt not responsible as they perceived their healthcare professional to be mainly responsible. We successfully used the COM-B model as a guide to identify facilitators and barriers of patients' adherence to multi-disease exacerbation action plans. Improving patients' adherence in future self-management interventions by targeting specific facilitators or barriers should be considered.

Gepubliceerd: Copd. 2023;20(1):262-73.
Impact factor: 2.2 ; Q4

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17. Geometrical Changes of the Aorta as Predictors for Thromboembolic Events After EVAR With the Anaconda Stent-Graft
Simmering JA, de Vries M, Haalboom M, Reijnen M, Slump CH, Geelkerken RH.

Purpose: Thromboembolic events (TE), including limb graft occlusion (LGO) and distal limb embolization (DLE), are common complications after endovascular aneurysm repair (EVAR). The aim of this study was to find predictors for TE in patients treated with the Anaconda stent-graft for infrarenal aneurysms.
Materials and methods: Geometrical and anatomical variables were retrospectively analyzed in a consecutive Anaconda cohort. Pre- and postoperative CT scans were used to derive geometrical parameters length, curvature, torsion, and tortuosity index (TI) from the center lumen lines (CLLs). Limb characteristics, pre-to-post EVAR and mid-term-follow-up changes in the parameters were evaluated for their predictive value for TE.
Results: Eighty-four patients (mean age 74±8.3 years, 74 men) were enrolled. The risk of TE was lowered with pre-to-post implant decreasing TI (steps of 0.05: OR: 1.30, 95% CI: 1.01-1.66, p=0.04), pre-to-post implant decreasing mean curvature (OR: 1.08, 95% CI: 1.01-1.16, p=0.03), and a larger degree of circumferential common iliac artery (CIA) calcification (OR: 0.98, 95% CI: 0.97-1.00, p=0.03). The only LGO predictor was the caudal relocation of maximal curvature after EVAR (OR: 1.01, 95% CI: 1.00-1.01, p=0.04). Preventors of DLE were CIA diameter (OR: 0.87, 95% CI: 0.76-0.99, p=0.04), circumferential CIA calcification (OR: 0.97, 95% CI: 0.95-1.00, p=0.03), mean and maximal curvature of the preoperative aortoiliac trajectory (OR: 0.86, 95% CI: 0.79-0.94, p<0.01 and OR: 0.97, 95% CI: 0.95-1.00, p=0.03, respectively) and pre-to-postoperative decrease in mean curvature (OR: 1.11, 95% CI: 1.02-1.21, p=0.02). Midterm TE predictors were length (OR: 0.95, 95% CI: 0.89-1.01, p=0.08) and torsion maximum location (OR: 1.01, 95% CI: 0.99-1.01, p=0.10).
Conclusion: The present study confirms that treatment of infrarenal AAA with an Anaconda stent-graft is related to a relatively high TE rate which decreases with a pre-to-postoperative reduction in curvature and TI, and a larger degree of circumferential CIA calcification. In other words, more aortoiliac straightening and more circumferential CIA calcification may prevent TE development after EVAR with this stent-graft.

Gepubliceerd: J Endovasc Ther. 2023;30(6):904-19.
Impact factor: 2.6 ; Q2

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18. eHealth Technologies for Monitoring Pediatric Asthma at Home: Scoping Review
van der Kamp MR, Hengeveld VS, Brusse-Keizer MGJ, Thio BJ, Tabak M.

Background: eHealth monitoring technologies offer opportunities to more objectively assess symptoms when they appear in daily life. Asthma is the most common chronic disease in childhood with an episodic course, requiring close follow-up of pediatric asthma control to identify disease deterioration, prevent exacerbations, and enhance quality of life. eHealth technologies in pediatric

asthma care show promising results regarding feasibility, acceptability, and asthma-related health outcomes. However, broad systematic evaluations of eHealth technologies in pediatric asthma are lacking.
Objective: The objective of this scoping review was to identify the types and applications of eHealth technologies for monitoring and treatment in pediatric asthma and explore which monitoring domains show the most relevance or potential for future research.
Methods: A scoping review was conducted using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. A systematic and comprehensive search was performed on English papers that investigated the development, validation, or application of eHealth technologies for home monitoring or treatment of pediatric asthma in the following databases: PubMed, Cochrane Library, IEEE, Scopus, CINAHL, PsycINFO, and ACM Digital Library. Two authors independently assessed eligibility and extracted data. Data were presented by a descriptive analysis of characteristics and a narrative report for each eHealth domain.
Results: The review included 370 manuscripts. The following 10 monitoring domains were identified: air quality, airway inflammation markers, lung function, physical activity, sleep, audiovisual, other physiological measurements, questionnaires, medication monitoring, and digital environment (ie, digital platforms, applications, websites, and software tools to monitor or support monitoring). Rising numbers of studies were seen, and the numbers accelerated in the last few years throughout most domains, especially medication monitoring and digital environment. Limited studies (35/370, 9.5%) of multiparameter monitoring strategies, using three or more domains, were found. The number of monitoring validation studies remained stable, while development and intervention studies increased. Intervention outcomes seemed to indicate the noninferiority and potential superiority of eHealth monitoring in pediatric asthma.
Conclusions: This systematic scoping review provides a unique overview of eHealth pediatric asthma monitoring studies, and it revealed that eHealth research takes place throughout different monitoring domains using different approaches. The outcomes of the review showed the potency for efficacy of most monitoring domains (especially the domains of medication monitoring, lung function, and digital environment). Future studies could focus on modifying potentially relevant hospital-based diagnostics for the home setting to investigate potential beneficial effects and focus on combining home-monitoring domains to facilitate multiparameter decision-making and personalized clinical decision support.

Gepubliceerd: J Med Internet Res. 2023;25:e45896.
Impact factor: 7.4 ; Q1

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19. Atrial fibrillation detected with outpatient cardiac rhythm monitoring in patients with ischemic stroke or TIA of undetermined cause
van der Maten G, Meijs MFL, van der Palen J, Brouwers P, von Birgelen C, van Opstal J, den Hertog HM.

Objectives: Guidelines advise cardiac rhythm monitoring for 3 up to 30 days for detecting atrial fibrillation (AF) in patients with ischemic stroke of undetermined cause. However, the optimal monitoring duration is unknown. We aimed to determine the AF detection rate during 7-day outpatient cardiac rhythm monitoring in this patient group.
Methods: Participants from a large tertiary hospital in a prospective observational study (ATTEST) underwent outpatient cardiac rhythm monitoring after a negative standard diagnostic evaluation (i.e., 12-lead electrocardiogram and in-hospital telemetry). Primary outcome was the rate of newly detected AF.
Results: We examined 373 patients [age: 67.8±11.6 years; women: 166(44.5%); stroke: 278(74.5%)]. Median monitoring duration was 7 days (Inter Quartile Range (IQR) 7-7), performed after median of 36 days (IQR 27-47). AF was newly detected in 17(4.6%) patients, 5.4% of patients with ischemic

stroke and 2.1% of patients with TIA. 53% of AF was detected on day-1, after day-3 73% of new AF was found. First AF episodes were detected up to day-7. Diabetes and increasing age were independent predictors of new AF.
Conclusion: After ischemic stroke or TIA of undetermined cause, 7-day outpatient cardiac rhythm monitoring detected new AF in 4.6%. Patients with AF had significantly more cardiovascular risk factors. Although about 50% of first AF episodes occurred during the first day of monitoring, new AF was detected up to day-7, implying that the recommended minimum of 3 days cardiac rhythm monitoring after ischemic stroke of undetermined cause is insufficient. Subsequent long-term rhythm monitoring should be considered in selected patients.

Gepubliceerd: J Stroke Cerebrovasc Dis. 2023;32(12):107400.
Impact factor: 2.5 ; Q3

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20. Artificial intelligence in systematic reviews: promising when appropriately used
van Dijk SHB, Brusse-Keizer MGJ, Bucsán CC, van der Palen J, Doggen CJM, Lenferink A.

Background: Systematic reviews provide a structured overview of the available evidence in medical-scientific research. However, due to the increasing medical-scientific research output, it is a time-consuming task to conduct systematic reviews. To accelerate this process, artificial intelligence (AI) can be used in the review process. In this communication paper, we suggest how to conduct a transparent and reliable systematic review using the AI tool 'ASReview' in the title and abstract screening.
Methods: Use of the AI tool consisted of several steps. First, the tool required training of its algorithm with several prelabelled articles prior to screening. Next, using a researcher-in-the-loop algorithm, the AI tool proposed the article with the highest probability of being relevant. The reviewer then decided on relevancy of each article proposed. This process was continued until the stopping criterion was reached. All articles labelled relevant by the reviewer were screened on full text.
Results: Considerations to ensure methodological quality when using AI in systematic reviews included: the choice of whether to use AI, the need of both deduplication and checking for inter-reviewer agreement, how to choose a stopping criterion and the quality of reporting. Using the tool in our review resulted in much time saved: only 23% of the articles were assessed by the reviewer.
Conclusion: The AI tool is a promising innovation for the current systematic reviewing practice, as long as it is appropriately used and methodological quality can be assured.

Gepubliceerd: BMJ Open. 2023;13(7):e072254.
Impact factor: 2.9 ; Q2

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21. Exploring Patterns of COPD Exacerbations and Comorbid Flare-Ups
van Dijk SHB, Brusse-Keizer MGJ, Effing T, van der Valk P, Ploumen EH, van der Palen J, Doggen CJM, Lenferink A.

Background: Comorbidities are known to complicate disease management in patients with Chronic Obstructive Pulmonary Disease (COPD). This is partly due to lack of insight into the interplay of acute exacerbations of COPD (AECOPD) and comorbid flare-ups. This study aimed to explore patterns of AECOPDs and comorbid flare-ups.
Methods: Data of increased symptoms were extracted from a 12-month daily symptom follow-up database including patients with COPD and comorbidities (chronic heart failure (CHF), anxiety, depression) and transformed to visualizations of AECOPDs and comorbid flare-up patterns over time. Patterns were subsequently categorized using an inductive approach, based on both predominance

(ie, which occurs most often) of AECOPDs or comorbid flare-ups, and their simultaneous (ie, simultaneous start in ≥ 50%) occurrence.
Results: We included 48 COPD patients (68 ± 9 years; comorbid CHF: 52%, anxiety: 40%, depression: 38%). In 25 patients with AECOPDs and CHF flare-ups, the following patterns were identified: AECOPDs predominant (n = 14), CHF flare-ups predominant (n = 5), AECOPDs nor CHF flare-ups predominant (n = 6). Of the 24 patients with AECOPDs and anxiety and/or depression flare-ups, anxiety and depression flare-ups occurred simultaneously in 15 patients. In 9 of these 24 patients, anxiety or depression flare-ups were observed independently from each other. In 31 of the included 48 patients, AECOPDs and comorbid flare-ups occurred mostly simultaneously.
Conclusion: Patients with COPD and common comorbidities show a variety of patterns of AECOPDs and comorbid flare-ups. Some patients, however, show repetitive patterns that could potentially be used to improve personalized disease management, if recognized.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis. 2023;18:2633-44.
Impact factor: 2.8 ; Q3

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22. Association of Country Income Level With the Characteristics and Outcomes of Critically Ill Patients Hospitalized With Acute Kidney Injury and COVID-19
Wainstein M, Spyrison N, Dai D, Ghadimi M, Chávez-Iñiguez JS, Rizo-Topete L, Citarella BW, Merson L, Pole JD, Claure-Del Granado R, Johnson DW, Shrapnel S, ISARIC Clinical Characterisation 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.

Introduction: Acute kidney injury (AKI) has been identified as one of the most common and significant problems in hospitalized patients with COVID-19. However, studies examining the relationship between COVID-19 and AKI in low- and low-middle income countries (LLMIC) are lacking. Given that AKI is known to carry a higher mortality rate in these countries, it is important to understand differences in this population.
Methods: This prospective, observational study examines the AKI incidence and characteristics of 32,210 patients with COVID-19 from 49 countries across all income levels who were admitted to an intensive care unit during their hospital stay.
Results: Among patients with COVID-19 admitted to the intensive care unit, AKI incidence was highest in patients in LLMIC, followed by patients in upper-middle income countries (UMIC) and high-income countries (HIC) (53%, 38%, and 30%, respectively), whereas dialysis rates were lowest among patients with AKI from LLMIC and highest among those from HIC (27% vs. 45%). Patients with AKI in LLMIC had the largest proportion of community-acquired AKI (CA-AKI) and highest rate of in-hospital death (79% vs. 54% in HIC and 66% in UMIC). The association between AKI, being from LLMIC and in-hospital death persisted even after adjusting for disease severity.
Conclusions: AKI is a particularly devastating complication of COVID-19 among patients from poorer nations where the gaps in accessibility and quality of healthcare delivery have a major impact on patient outcomes.

Gepubliceerd: Kidney Int Rep. 2023;8(8):1514-30.
Impact factor: 6.0 ; Q1

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23. 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. 2023;164:111084.
Impact factor: 4.7 ; Q2

Totale impact factor: 108.1
Gemiddelde impact factor: 4.7

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 18.0
Gemiddelde impact factor: 4.5

Microbiologie

1. Implementation of Recommendations on the Use of Corticosteroids in Severe COVID-19
Camirand-Lemyre F, Merson L, Tirupakuzhi Vijayaraghavan BK, Burrell AJC, Citarella BW, Domingue MP, Lévesque S, Usuf E, Wils EJ, Ohshimo S, Martin-Loeches I, Sandulescu O, Laake JH, Lamontagne F, ISARIC Clinical Characterisation 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.

Importance: Research diversity and representativeness are paramount in building trust, generating valid biomedical knowledge, and possibly in implementing clinical guidelines.
Objectives: To compare variations over time and across World Health Organization (WHO) geographic regions of corticosteroid use for treatment of severe COVID-19; secondary objectives were to evaluate the association between the timing of publication of the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial (June 2020) and the WHO guidelines for corticosteroids (September 2020) and the temporal trends observed in corticosteroid use by region and to describe the geographic distribution of the recruitment in clinical trials that informed the WHO recommendation.
Design, setting, and participants: This prospective cohort study of 434 851 patients was conducted between January 31, 2020, and September 2, 2022, in 63 countries worldwide. The data were collected under the auspices of the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC)-WHO Clinical Characterisation Protocol for Severe Emerging Infections. Analyses were restricted to patients hospitalized for severe COVID-19 (a subset of the ISARIC data set).
Exposure: Corticosteroid use as reported to the ISARIC-WHO Clinical Characterisation Protocol for Severe Emerging Infections.
Main outcomes and measures: Number and percentage of patients hospitalized with severe COVID-19 who received corticosteroids by time period and by WHO geographic region.
Results: Among 434 851 patients with confirmed severe or critical COVID-19 for whom receipt of corticosteroids could be ascertained (median [IQR] age, 61.0 [48.0-74.0] years; 53.0% male), 174 307 (40.1%) received corticosteroids during the study period. Of the participants in clinical trials that informed the guideline, 91.6% were recruited from the United Kingdom. In all regions, corticosteroid use for severe COVID-19 increased, but this increase corresponded to the timing of the RECOVERY trial (time-interruption coefficient 1.0 [95% CI, 0.9-1.2]) and WHO guideline (time-interruption coefficient 1.9 [95% CI, 1.7-2.0]) publications only in Europe. At the end of the study period, corticosteroid use for treatment of severe COVID-19 was highest in the Americas (5421 of 6095 [88.9%]; 95% CI, 87.7-90.2) and lowest in Africa (31 588 of 185 191 [17.1%]; 95% CI, 16.8-17.3).
Conclusions and relevance: The results of this cohort study showed that implementation of the guidelines for use of corticosteroids in the treatment of severe COVID-19 varied geographically. Uptake of corticosteroid treatment was lower in regions with limited clinical trial involvement. Improving research diversity and representativeness may facilitate timely knowledge uptake and guideline implementation.

Gepubliceerd: JAMA Netw Open. 2023;6(12):e2346502.
Impact factor: 13.8 ; Q1

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2. Neurological manifestations of COVID-19 in adults and children
Cho SM, White N, Premraj L, Battaglini D, Fanning J, Suen J, Bassi GL, Fraser J, Robba C, Griffee M, Singh B, Citarella BW, Merson L, Solomon T, Thomson D, ISARIC Clinical Characterisation 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.

Different neurological manifestations of coronavirus disease 2019 (COVID-19) in adults and children and their impact have not been well characterized. We aimed to determine the prevalence of neurological manifestations and in-hospital complications among hospitalized COVID-19 patients and ascertain differences between adults and children. We conducted a prospective multicentre observational study using the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) cohort across 1507 sites worldwide from 30 January 2020 to 25 May 2021. Analyses of neurological manifestations and neurological complications considered unadjusted prevalence estimates for predefined patient subgroups, and adjusted estimates as a function of patient age and time of hospitalization using generalized linear models. Overall, 161 239 patients (158 267 adults; 2972 children) hospitalized with COVID-19 and assessed for neurological manifestations and complications were included. In adults and children, the most frequent neurological manifestations at admission were fatigue (adults: 37.4%; children: 20.4%), altered consciousness (20.9%; 6.8%), myalgia (16.9%; 7.6%), dysgeusia (7.4%; 1.9%), anosmia (6.0%; 2.2%) and seizure (1.1%; 5.2%). In adults, the most frequent in-hospital neurological complications were stroke (1.5%), seizure (1%) and CNS infection (0.2%). Each occurred more frequently in intensive care unit (ICU) than in non-ICU patients. In children, seizure was the only neurological complication to occur more frequently in ICU versus non-ICU (7.1% versus 2.3%, $P < 0.001$). Stroke prevalence increased with increasing age, while CNS infection and seizure steadily decreased with age. There was a dramatic decrease in stroke over time during the pandemic. Hypertension, chronic neurological disease and the use of extracorporeal membrane oxygenation were associated with increased risk of stroke. Altered consciousness was associated with CNS infection, seizure and stroke. All in-hospital neurological complications were associated with increased odds of death. The likelihood of death rose with increasing age, especially after 25 years of age. In conclusion, adults and children have different neurological manifestations and in-hospital complications associated with COVID-19. Stroke risk increased with increasing age, while CNS infection and seizure risk decreased with age.

Gepubliceerd: Brain. 2023;146(4):1648-61.
Impact factor: 14.5 ; Q1

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3. Thrombotic and hemorrhagic complications of COVID-19 in adults hospitalized in high-income countries compared with those in adults hospitalized in low- and middle-income countries in an international registry

Griffee MJ, Bozza PT, Reyes LF, Eddington DP, Rosenberger D, Merson L, Citarella BW, Fanning JP, Alexander PMA, Fraser J, Dalton H, Cho SM, ISARIC Clinical Characterisation 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: COVID-19 has been associated with a broad range of thromboembolic, ischemic, and hemorrhagic complications (coagulopathy complications). Most studies have focused on patients with severe disease from high-income countries (HICs).
Objectives: The main aims were to compare the frequency of coagulopathy complications in developing countries (low- and middle-income countries [LMICs]) with those in HICs, delineate the frequency across a range of treatment levels, and determine associations with in-hospital mortality.
Methods: Adult patients enrolled in an observational, multinational registry, the International Severe Acute Respiratory and Emerging Infections COVID-19 study, between January 1, 2020, and September 15, 2021, met inclusion criteria, including admission to a hospital for laboratory-confirmed, acute COVID-19 and data on complications and survival. The advanced-treatment cohort received care, such as admission to the intensive care unit, mechanical ventilation, or inotropes or vasopressors; the basic-treatment cohort did not receive any of these interventions.
Results: The study population included 495,682 patients from 52 countries, with 63% from LMICs and 85% in the basic treatment cohort. The frequency of coagulopathy complications was higher in HICs

(0.76%-3.4%) than in LMICs (0.09%-1.22%). Complications were more frequent in the advanced-treatment cohort than in the basic-treatment cohort. Coagulopathy complications were associated with increased in-hospital mortality (odds ratio, 1.58; 95% CI, 1.52-1.64). The increased mortality associated with these complications was higher in LMICs (58.5%) than in HICs (35.4%). After controlling for coagulopathy complications, treatment intensity, and multiple other factors, the mortality was higher among patients in LMICs than among patients in HICs (odds ratio, 1.45; 95% CI, 1.39-1.51).
Conclusion: In a large, international registry of patients hospitalized for COVID-19, coagulopathy complications were more frequent in HICs than in LMICs (developing countries). Increased mortality associated with coagulopathy complications was of a greater magnitude among patients in LMICs. Additional research is needed regarding timely diagnosis of and intervention for coagulation derangements associated with COVID-19, particularly for limited-resource settings.

Gepubliceerd: Res Pract Thromb Haemost. 2023;7(5):102142.
Impact factor: 4.6 ; Q2

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4. Characteristics and outcomes of an international cohort of 600 000 hospitalized patients with COVID-19
Kartsonaki C, Baillie JK, Barrio NG, Baruch J, Beane A, Blumberg L, Bozza F, Broadley T, Burrell A, Carson G, Citarella BW, Dagens A, Dankwa EA, Donnelly CA, Dunning J, Elotmani L, Escher M, Farshait N, Goffard JC, Gonçalves BP, Hall M, Hashmi M, Sim Lim Heng B, Ho A, Jassat W, Pedrera Jiménez M, Laouenan C, Lissauer S, Martin-Loeches I, Mentré F, Merson L, Morton B, Munblit D, Nekliudov NA, Nichol AD, Singh Oinam BC, Ong D, Panda PK, Petrovic M, Pritchard MG, Ramakrishnan N, Ramos GV, Roger C, Sandulescu O, Semple MG, Sharma P, Sigfrid L, Somers EC, Streinu-Cercel A, Taccone F, Vecham PK, Kumar Tirupakuzhi Vijayaraghavan B, Wei J, Wils EJ, Ci Wong X, Horby P, Rojek A, Olliaro PL, ISARIC Clinical Characterisation 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: We describe demographic features, treatments and clinical outcomes in the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) COVID-19 cohort, one of the world's largest international, standardized data sets concerning hospitalized patients.
Methods: The data set analysed includes COVID-19 patients hospitalized between January 2020 and January 2022 in 52 countries. We investigated how symptoms on admission, co-morbidities, risk factors and treatments varied by age, sex and other characteristics. We used Cox regression models to investigate associations between demographics, symptoms, co-morbidities and other factors with risk of death, admission to an intensive care unit (ICU) and invasive mechanical ventilation (IMV).
Results: Data were available for 689 572 patients with laboratory-confirmed (91.1%) or clinically diagnosed (8.9%) SARS-CoV-2 infection from 52 countries. Age [adjusted hazard ratio per 10 years 1.49 (95% CI 1.48, 1.49)] and male sex [1.23 (1.21, 1.24)] were associated with a higher risk of death. Rates of admission to an ICU and use of IMV increased with age up to age 60 years then dropped. Symptoms, co-morbidities and treatments varied by age and had varied associations with clinical outcomes. The case-fatality ratio varied by country partly due to differences in the clinical characteristics of recruited patients and was on average 21.5%.
Conclusions: Age was the strongest determinant of risk of death, with a ∼30-fold difference between the oldest and youngest groups; each of the co-morbidities included was associated with up to an almost 2-fold increase in risk. Smoking and obesity were also associated with a higher risk of death. The size of our international database and the standardized data collection method make this study a comprehensive international description of COVID-19 clinical features. Our findings may inform strategies that involve prioritization of patients hospitalized with COVID-19 who have a higher risk of death.

Gepubliceerd: Int J Epidemiol. 2023;52(2):355-76.
Impact factor: 7.7 ; Q1

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5. Association of Country Income Level With the Characteristics and Outcomes of Critically Ill Patients Hospitalized With Acute Kidney Injury and COVID-19
Wainstein M, Spyrison N, Dai D, Ghadimi M, Chávez-Iñiguez JS, Rizo-Topete L, Citarella BW, Merson L, Pole JD, Claure-Del Granado R, Johnson DW, Shrapnel S, ISARIC Clinical Characterisation 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.

Introduction: Acute kidney injury (AKI) has been identified as one of the most common and significant problems in hospitalized patients with COVID-19. However, studies examining the relationship between COVID-19 and AKI in low- and low-middle income countries (LLMIC) are lacking. Given that AKI is known to carry a higher mortality rate in these countries, it is important to understand differences in this population.
Methods: This prospective, observational study examines the AKI incidence and characteristics of 32,210 patients with COVID-19 from 49 countries across all income levels who were admitted to an intensive care unit during their hospital stay.
Results: Among patients with COVID-19 admitted to the intensive care unit, AKI incidence was highest in patients in LLMIC, followed by patients in upper-middle income countries (UMIC) and high-income countries (HIC) (53%, 38%, and 30%, respectively), whereas dialysis rates were lowest among patients with AKI from LLMIC and highest among those from HIC (27% vs. 45%). Patients with AKI in LLMIC had the largest proportion of community-acquired AKI (CA-AKI) and highest rate of in-hospital death (79% vs. 54% in HIC and 66% in UMIC). The association between AKI, being from LLMIC and in-hospital death persisted even after adjusting for disease severity.
Conclusions: AKI is a particularly devastating complication of COVID-19 among patients from poorer nations where the gaps in accessibility and quality of healthcare delivery have a major impact on patient outcomes.

Gepubliceerd: Kidney Int Rep. 2023;8(8):1514-30.
Impact factor: 6.0 ; Q1

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6. Foul smelling urine in an adult caused by Aerococcus urinae
Geeraedts F, Stoffers C, Smidt H, Schijffelen M.

We describe the first adult case with Aerococcus urinae positive urine cultures as the proven cause of recurrent socially disabling malodorous urine. Bacterial strain specific factors as well as host factors are shown to play a role. The condition can be resolved with proper antibiotics.

Gepubliceerd: IDCases 2022:31:e01657
Impact factor 1.5 ; Q4

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7. Impact of reduced antibiotic treatment duration on antimicrobial resistance in critically ill patients in the randomized controlled SAPS-trial
Shajiei A, Berends MS, Luz CF, van Oers JA, Harmsen HJM, Vos P, Klont R, Loef BG, Reidinga AC, Bormans-Russell L, Linsen K, Dormans T, Otten M, van der Bij, A, Beishuizen A, de Lange DW, de Jong E, Nijsten MW.

Background: In the previously reported SAPS trial (https://clinicaltrials.gov/ct2/show/NCT01139489), procalcitonin-guidance safely reduced the duration of antibiotic treatment in critically ill patients. We assessed the impact of shorter antibiotic treatment on antimicrobial resistance development in SAPS patients.
Materials and methods: Cultures were assessed for the presence of multi-drug resistant (MDR) or highly resistant organisms (HRMO) and compared between PCT-guided and control patients. Baseline isolates from 30 days before to 5 days after randomization were compared with those from 5 to 30 days post-randomization. The primary endpoint was the incidence of new MDR/HRMO positive patients.
Results: In total, 8,113 cultures with 96,515 antibiotic test results were evaluated for 439 and 482 patients randomized to the PCT and control groups, respectively. Disease severity at admission was similar for both groups. Median (IQR) durations of the first course of antibiotics were 6 days (4-10) and 7 days (5-11), respectively (p = 0.0001). Antibiotic-free days were 7 days (IQR 0-14) and 6 days (0-13; p = 0.05). Of all isolates assessed, 13% were MDR/HRMO positive and at baseline 186 (20%) patients were MDR/HMRO-positive. The incidence of new MDR/HRMO was 39 (8.9%) and 45 (9.3%) in PCT and control patients, respectively (p = 0.82). The time courses for MDR/HRMO development were also similar for both groups (p = 0.33).
Conclusions: In the 921 randomized patients studied, the small but statistically significant reduction in antibiotic treatment in the PCT-group did not translate into a detectable change in antimicrobial resistance. Studies with larger differences in antibiotic treatment duration, larger study populations or populations with higher MDR/HRMO incidences might detect such differences.

Gepubliceerd: Front Med (Lausanne) 2023:10:1080007.
Impact factor: 2.9 ; Q2

Totale impact factor: 52.0
Gemiddelde impact factor: 7.4

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 1
Totale impact factor: 1.5
Gemiddelde impact factor: 1.5

MKA chirurgie

1. [Temporomandibular joint dysfunction as a result of a condylar metastasis]
Klijn RJ, Huizinga MP, van Bemmel AJM.

An 83-year-old man reported recent temporomandibular joint complaints and a swelling near his ear. The swelling moved whileopening the mouth. Additional imaging showed an osseous deviation of the right condyle with extension into the masticator space. In addition, several lytic and expansive bone lesions were visible in the skeleton, which initially suggested multiple myeloma. However, blood tests pointed in the direction of prostate cancer that had been treated twenty years earlier. There appeared to be extensive osseous metastatic recurrent prostate carcinoma with a metastasis in the right condyle of the mandible. The patient was treated with palliative systemic therapy.

Gepubliceerd: Ned Tijdschr Tandheelkd. 2023;130(4):161-4.
Impact factor: onbekend

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2. Efficacy and Toxicity of Calcitonin Treatment in Children with Cherubism: A Single-Center Cohort Study
Schreuder WH, Meijer EB, Cleven AHG, Edelenbos E, Klop C, Schreurs R, de Jong RT, van Maarle MC, Horsthuis RBG, de Lange J, van den Berg H.

Cherubism is a rare autosomal dominant disease characterized by expansile osteolytic jawbone lesions. The effect and safety of off-label calcitonin treatment during the progressive phase of the disease are not well described. In this retrospective study, we present data on the radiological response and adverse effects of subcutaneously administered calcitonin in a cohort of nine cherubism children (three female, six male). Two of the nine patients underwent two separate treatment courses with a significant off-treatment interval in between; therefore, a total of 11 treatment courses with a mean duration of 17.9 months (range <1 to 35, SD 10.8) were studied. To measure the response, the cumulative volume of cherubism lesions was calculated from available three-dimensional imaging. The primary outcome was the change in the volume of lesions during calcitonin treatment and only assessed for the eight treatment courses with a minimal duration of 6 months. A statistically significant reduction in the mean cumulative volume of lesions was seen regardless of treatment duration. Average volume reduction was highest in the first half year of treatment, with a gradual, ongoing reduction thereafter. For the secondary outcome, the change in the cumulative volume of lesions after treatment cessation was assessed for the seven treatment courses with follow-up imaging available. After six of these seven treatment courses, the cumulative volume increased again but remained undoubtedly smaller than the initial volume at the start of therapy. Adverse effects were assessed for all 11 treatment courses and occurred in 73% of them. Most adverse effects were mild and low grade, with the most severe being one grade 3 symptomatic hypocalcemia requiring hospitalization and early treatment termination. Calcitonin treatment seems effective and tolerable in treating actively progressing cherubism in children. However, further research is required to better understand the pharmacological treatment of cherubism, including also other drugs, dosing, and protocols.

Gepubliceerd: J Bone Miner Res. 2023;38(12):1822-33.
Impact factor: 6.2 ; Q1

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3. Patients' and Healthcare Professionals' Perspectives on Better Use of Patient-Reported Outcome Measures in Head and Neck Cancer
de Jel DVC, Young-Afat DA, Ooms-Renckens MM, Smeele LE, Rakhorst HA, DHNA study group: van Bemmel AJM

Objectives: Patients with head and neck cancer (HNC) are often highly affected by disease and treatment, resulting in impaired physical functioning and quality of life. Therefore, evaluation of patients' psychosocial and functional outcomes can be facilitated by patient-reported outcome measures (PROMs). By providing the patients' own perspectives, PROMs are crucial to improving patient-centered care. This study aimed to improve understanding of the perceived value of PROMs in HNC care and how to optimize their clinical value based on patients' and multidisciplinary healthcare professionals' (HCPs) perspectives.
Methods: Population-based surveys among patients with HNC through their patient association and among HCPs nationwide through the Dutch Head and Neck Audit.
Results: A total of 54 patients and 40 multidisciplinary HCPs from all 14 nationwide HNC centers (100%) responded. For patients, the most important element of patient-reported outcome collection systems was including a call to action for those with worse-than-average scores (28%), whereas clinicians found discussing scores during clinical visits the most important (39%). Although 16% of clinicians found short completion time the most important element, none of the patients selected completion time as most important. Additionally, 17% of patients stated completion time was not an issue, provided clinicians would use the outcomes for clinical purposes.
Conclusions: Although patients and clinicians acknowledged the value of patient-reported outcomes, patients would like to be more involved in the clinical implications of their outcomes. Enhancing patients' involvement by a call to action and providing feedback on their scores during outpatient clinic visits may improve the clinical value of PROMs.

Gepubliceerd: Value Health. 2023;26(8):1210-6.
Impact factor: 4.5 ; Q1

Totale impact factor: 10.7
Gemiddelde impact factor: 3.6

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: NVT (onbekend)
Gemiddelde impact factor: NVT

Neurocentrum

1. Validity of Early Outcomes as Indicators for Comparing Hospitals on Quality of Stroke Care
Amini M, Eijkenaar F, Lingsma HF, den Hartog SJ, Olthuis SGH, Martens J, van der Worp B, van Zwam W, van der Hoorn A, Roosendaal SD, Roozenbeek B, Dippel D, van Leeuwen N, MR CLEAN Registry Investigators: Brouwers P, Bulut T.

Background: Insight into outcome variation between hospitals could help to improve quality of care. We aimed to assess the validity of early outcomes as quality indicators for acute ischemic stroke care for patients treated with endovascular therapy (EVT).
Methods and Results: We used data from the MR CLEAN (Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry, a large multicenter prospective cohort study including 3279 patients with acute ischemic stroke undergoing EVT. Random effect linear and proportional odds regression were used to analyze the effect of case mix on between-hospital differences in 2 early outcomes: the National Institutes of Health Stroke Scale (NIHSS) score at 24 to 48 hours and the expanded thrombolysis in cerebral infarction score. Between-hospital variation in outcomes was assessed using the variance of random hospital effects (tau(2)). In addition, we estimated the correlation between hospitals' EVT-patient volume and (case-mix-adjusted) outcomes. Both early outcomes and case-mix characteristics varied significantly across hospitals. Between-hospital variation in the expanded thrombolysis in cerebral infarction score was not influenced by case-mix adjustment (tau (2)=0.17 in both models). In contrast, for the NIHSS score at 24 to 48 hours, case-mix adjustment led to a decrease in variation between hospitals (tau (2) decreases from 0.19 to 0.17). Hospitals' EVT-patient volume was strongly correlated with higher expanded thrombolysis in cerebral infarction scores (r=0.48) and weakly with lower NIHSS score at 24 to 48 hours (r=0.15).
Conclusions: Between-hospital variation in NIHSS score at 24 to 48 hours is significantly influenced by case-mix but not by patient volume. In contrast, between-hospital variation in expanded thrombolysis in cerebral infarction score is strongly influenced by EVT-patient volume but not by case-mix. Both outcomes may be suitable for comparing hospitals on quality of care, provided that adequate adjustment for case-mix is applied for NIHSS score.

Gepubliceerd: J Am Heart Assoc. 2023;12(8):e027647.
Impact factor: 5.4 ; Q2

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2. The International Cardiac Arrest Research (I-CARE) Consortium Electroencephalography Database
Amorim E, Zheng WL, Ghassemi MM, Aghaeeaval M, Kandhare P, Karukonda V, Lee JW, Herman ST, Sivaraju A, Gaspard N, Hofmeijer J, van Putten M, Sameni R, Reyna MA, Clifford GD, Westover MB.

Objective: To develop a harmonized multicenter clinical and electroencephalography (EEG) database for acute hypoxic-ischemic brain injury research involving patients with cardiac arrest.
Design: Multicenter cohort, partly prospective and partly retrospective.
Setting: Seven academic or teaching hospitals from the U.S. and Europe.
Patients: Individuals aged 16 or older who were comatose after return of spontaneous circulation following a cardiac arrest who had continuous EEG monitoring were included.
Interventions: not applicable.
Measurements and main results: Clinical and EEG data were harmonized and stored in a common Waveform Database (WFDB)-compatible format. Automated spike frequency, background continuity, and artifact detection on EEG were calculated with 10 second resolution and summarized hourly. Neurological outcome was determined at 3-6 months using the best Cerebral Performance Category

(CPC) scale. This database includes clinical and 56,676 hours (3.9 TB) of continuous EEG data for 1,020 patients. Most patients died (N=603, 59%), 48 (5%) had severe neurological disability (CPC 3 or 4), and 369 (36%) had good functional recovery (CPC 1-2). There is significant variability in mean EEG recording duration depending on the neurological outcome (range 53-102h for CPC 1 and CPC 4, respectively). Epileptiform activity averaging 1 Hz or more in frequency for at least one hour was seen in 258 (25%) patients (19% for CPC 1-2 and 29% for CPC 3-5). Burst suppression was observed for at least one hour in 207 (56%) and 635 (97%) patients with CPC 1-2 and CPC 3-5, respectively.
Conclusions: The International Cardiac Arrest Research (I-CARE) consortium database provides a comprehensive real-world clinical and EEG dataset for neurophysiology research of comatose patients after cardiac arrest. This dataset covers the spectrum of abnormal EEG patterns after cardiac arrest, including epileptiform patterns and those in the ictal-interictal continuum.

Gepubliceerd: medRxiv. 2023.
Impact factor: onbekend

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3. The International Cardiac Arrest Research Consortium Electroencephalography Database (Update)
Amorim E, Zheng WL, Ghassemi MM, Aghaeeaval M, Kandhare P, Karukonda V, Lee JW, Herman ST, Sivaraju A, Gaspard N, Hofmeijer J, van Putten M, Sameni R, Reyna MA, Clifford GD, Westover MB.

Objectives: To develop the International Cardiac Arrest Research (I-CARE), a harmonized multicenter clinical and electroencephalography database for acute hypoxic-ischemic brain injury research involving patients with cardiac arrest.
Design: Multicenter cohort, partly prospective and partly retrospective.
Setting: Seven academic or teaching hospitals from the United States and Europe.
Patients: Individuals 16 years old or older who were comatose after return of spontaneous circulation following a cardiac arrest who had continuous electroencephalography monitoring were included.
Interventions: Not applicable.
Measurements and main results: Clinical and electroencephalography data were harmonized and stored in a common Waveform Database-compatible format. Automated spike frequency, background continuity, and artifact detection on electroencephalography were calculated with 10-second resolution and summarized hourly. Neurologic outcome was determined at 3-6 months using the best Cerebral Performance Category (CPC) scale. This database includes clinical data and 56,676 hours (3.9 terabytes) of continuous electroencephalography data for 1,020 patients. Most patients died (n = 603, 59%), 48 (5%) had severe neurologic disability (CPC 3 or 4), and 369 (36%) had good functional recovery (CPC 1-2). There is significant variability in mean electroencephalography recording duration depending on the neurologic outcome (range, 53-102 hr for CPC 1 and CPC 4, respectively). Epileptiform activity averaging 1 Hz or more in frequency for at least 1 hour was seen in 258 patients (25%) (19% for CPC 1-2 and 29% for CPC 3-5). Burst suppression was observed for at least 1 hour in 207 (56%) and 635 (97%) patients with CPC 1-2 and CPC 3-5, respectively.
Conclusions: The I-CARE consortium electroencephalography database provides a comprehensive real-world clinical and electroencephalography dataset for neurophysiology research of comatose patients after cardiac arrest. This dataset covers the spectrum of abnormal electroencephalography patterns after cardiac arrest, including epileptiform patterns and those in the ictal-interictal continuum.

Gepubliceerd: Crit Care Med. 2023;51(12):1802-11.
Impact factor: 8.8 ; Q1

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4. Neurophysiology State Dynamics Underlying Acute Neurologic Recovery After Cardiac Arrest
Amorim E, Zheng WL, Jing J, Ghassemi MM, Lee JW, Wu O, Herman ST, Pang T, Sivaraju A, Gaspard N, Hirsch L, Ruijter BJ, Tjepkema-Cloostermans MC, Hofmeijer J, van Putten M, Westover MB.

Background and objectives: Epileptiform activity and burst suppression are neurophysiology signatures reflective of severe brain injury after cardiac arrest. We aimed to delineate the evolution of coma neurophysiology feature ensembles associated with recovery from coma after cardiac arrest.
Methods: Adults in acute coma after cardiac arrest were included in a retrospective database involving 7 hospitals. The combination of 3 quantitative EEG features (burst suppression ratio [BSup], spike frequency [SpF], and Shannon entropy [En]) was used to define 5 distinct neurophysiology states: epileptiform high entropy (EHE: SpF ≥4 per minute and En ≥5); epileptiform low entropy (ELE: SpF ≥4 per minute and <5 En); nonepileptiform high entropy (NEHE: SpF <4 per minute and ≥5 En); nonepileptiform low entropy (NELE: SpF <4 per minute and <5 En), and burst suppression (BSup ≥50% and SpF <4 per minute). State transitions were measured at consecutive 6-hour blocks between 6 and 84 hours after return of spontaneous circulation. Good neurologic outcome was defined as best cerebral performance category 1-2 at 3-6 months.
Results: One thousand thirty-eight individuals were included (50,224 hours of EEG), and 373 (36%) had good outcome. Individuals with EHE state had a 29% rate of good outcome, while those with ELE had 11%. Transitions out of an EHE or BSup state to an NEHE state were associated with good outcome (45% and 20%, respectively). No individuals with ELE state lasting >15 hours had good recovery.
Discussion: Transition to high entropy states is associated with an increased likelihood of good outcome despite preceding epileptiform or burst suppression states. High entropy may reflect mechanisms of resilience to hypoxic-ischemic brain injury.

Gepubliceerd: Neurology. 2023;101(9):e940-e52.
Impact factor: 10.1 ; Q1

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5. Thrombus imaging characteristics within acute ischemic stroke: similarities and interdependence
Arrarte Terreros N, Bruggeman AA, Kappelhof M, Tolhuisen ML, Brouwer J, Hoving JW, Konduri PR, van Kranendonk KR, Dutra BG, Alves HC, Dippel DW, van Zwam WH, Beenen LF, Yo LS, van Bavel E, Majoie CB, Marquering HA, MR CLEAN Registry Investigators: Brouwers P, Bulut T.

Background: The effects of thrombus imaging characteristics on procedural and clinical outcomes after ischemic stroke are increasingly being studied. These thrombus characteristics - for eg, size, location, and density - are commonly analyzed as separate entities. However, it is known that some of these thrombus characteristics are strongly related. Multicollinearity can lead to unreliable prediction models. We aimed to determine the distribution, correlation and clustering of thrombus imaging characteristics based on a large dataset of anterior-circulation acute ischemic stroke patients.
Methods: We measured thrombus imaging characteristics in the MR CLEAN Registry dataset, which included occlusion location, distance from the intracranial carotid artery to the thrombus (DT), thrombus length, density, perviousness, and clot burden score (CBS). We assessed intercorrelations with Spearman's coefficient (ρ) and grouped thrombi based on 1) occlusion location and 2) thrombus length, density and perviousness using unsupervised clustering.
Results: We included 934 patients, of which 22% had an internal carotid artery (ICA) occlusion, 61% M1, 16% M2, and 1% another occlusion location. All thrombus characteristics were significantly correlated. Higher CBS was strongly correlated with longer DT ($\rho=0.67$, $p<0.01$), and moderately correlated with shorter thrombus length ($\rho=-0.41$, $p<0.01$). In more proximal occlusion locations, thrombi were significantly longer, denser, and less pervious. Unsupervised clustering analysis resulted in four thrombus groups; however, the cohesion within and distinction between the groups were weak.

Conclusions: Thrombus imaging characteristics are significantly intercorrelated - strong correlations should be considered in future predictive modeling studies. Clustering analysis showed there are no distinct thrombus archetypes - novel treatments should consider this thrombus variability.

Gepubliceerd: J Neurointerv Surg. 2023;15(e1):e60-e8.
Impact factor: 4.9 ; Q1

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6. Bifurcation occlusions and endovascular treatment outcome in acute ischemic stroke
Arrarte Terreros N, Bruggeman AAE, van Voorst H, Konduri PR, Jansen IGH, Kappelhof M, Tolhuisen ML, Boodt N, Dippel DWJ, van der Lugt A, van Zwam WH, van Oostenbrugge RJ, van der Worp HB, Emmer BJ, Meijer FJA, Roos Y, van Bavel E, Marquering HA, Majoie C, MR Clean Investigators: Brouwers P, Bulut T.

Background: A thrombus in the M1 segment of the middle cerebral artery (MCA) can occlude this main stem only or extend into the M1-M2 bifurcation. The occlusion pattern may affect endovascular treatment (EVT) success, as a bifurcated thrombus may be more prone to fragmentation during retrieval.
Objective: To investigate whether bifurcated thrombus patterns are associated with EVT procedural and clinical outcomes.
Methods: Occlusion patterns of MCA thrombi on CT angiography from MR CLEAN Registry patients were classified into three groups: main stem occlusion, bifurcation occlusion extending into one M2 branch, and bifurcation occlusion extending into both M2 branches. Procedural parameters, procedural outcomes (reperfusion grade and embolization to new territory), and clinical outcomes (24-48 hour National Institutes of Health Stroke Scale [$NIHSS_{FU}$] score, change in NIHSS scores between 24 and 48 hours and baseline Δ [NIHSS], and 90-day modified Rankin Scale [mRS] scores) were compared between occlusion patterns.
Results: We identified 1023 patients with an MCA occlusion of whom 370 (36%) had a main stem occlusion, 151 (15%) a single branch, and 502 (49%) a double branch bifurcation occlusion. There were no statistically significant differences in retrieval method, procedure time, number of retrieval attempts, reperfusion grade, and embolization to new territory between occlusion patterns. Patients with main stem occlusions had lower $NIHSS_{FU}$ scores than patients with single (7 vs 11, p=0.01) or double branch occlusions (7 vs 9, p=0.04). However, there were no statistically significant differences in Δ NIHSS or in 90-day mRS scores.
Conclusions: In our population, EVT procedural and long-term clinical outcomes were similar for MCA bifurcation occlusions and MCA main stem occlusions.

Gepubliceerd: J Neurointerv Surg. 2023;15(4):355-62.
Impact factor: 4.9 ; Q1

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7. Neurophysiological signatures reflect differences in visual attention during absence seizures
Barone V, Piastra MC, van Dijk JP, Visser GH, Debeij-van Hall M, van Putten M.

Objective: Absences affect visual attention and eye movements variably. Here, we explore whether the dissimilarity of these symptoms during absences is reflected in differences in electroencephalographic (EEG) features, functional connectivity, and activation of the frontal eye field.
Methods: Pediatric patients with absences performed a computerized choice reaction time task, with simultaneous recording of EEG and eye-tracking. We quantified visual attention and eye movements

with reaction times, response correctness, and EEG features. Finally, we studied brain networks involved in the generation and propagation of seizures.
Results: Ten pediatric patients had absences during the measurement. Five patients had preserved eye movements (preserved group) and five patients showed disrupted eye movements (unpreserved group) during seizures. Source reconstruction showed a stronger involvement of the right frontal eye field during absences in the unpreserved group than in the preserved group (dipole fraction 1.02% and 0.34%, respectively, $p < 0.05$). Graph analysis revealed different connection fractions of specific channels.
Conclusions: The impairment of visual attention varies among patients with absences and is associated with differences in EEG features, network activation, and involvement of the right frontal eye field.
Significance: Assessing the visual attention of patients with absences can be usefully employed in clinical practice for tailored advice to the individual patient.

Gepubliceerd: Clin Neurophysiol. 2023;152:34-42.
Impact factor: 4.7 ; Q1

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8. 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. 2023;54(5):512-21.
Impact factor: 2.0 ; Q4

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9. The cognitive status of chronic subdural hematoma patients after treatment: an exploratory study
Blaauw J, Hertog HMD, Holl DC, Thüss NS, van der Gaag NA, Jellema K, Dammers R, Kho KH, Groen RJM, Lingsma HF, Jacobs B, van der Naalt J.

Objective: Chronic subdural hematoma (CSDH) is a common neurological condition, often affecting the elderly. Cognitive impairment is frequently observed at presentation. However, the course and longer term aspects of the cognitive status of CSDH patients are unknown. In this study, we aim to explore the cognitive status of CSDH patients after treatment.
Methods: An exploratory study in which CSDH patients were assessed 3 months after treatment and compared to healthy controls. A total of 56 CSDH patients (age 72.1 SD ± 10.8 years with 43 [77%]

males) and 60 healthy controls were included (age 67.5 ± SD 4.8 with 34 [57%] males). Cognitive testing was performed using the Telephonic Interview of Cognitive Status-modified (TICS-m), a 12-item questionnaire in which a total of 50 points can be obtained on several cognitive domains.
Results: Median time between treatment and cognitive testing was 93 days (range 76-139). TICS-m scores of CSDH patients were significantly lower than healthy controls, after adjusting for age and sex: mean score 34.6 (95% CI: 33.6-35.9) vs. 39.6 (95% CI: 38.5-40.7), p value < 0.001. More than half (54%) of CSDH patients have cognitive scores at follow-up that correspond with cognitive impairment.
Conclusion: A large number of CSDH patients show significantly worse cognitive status 3 months after treatment compared to healthy controls. This finding underlines the importance of increased awareness for impaired cognition after CSDH. Further research on this topic is warranted.

Gepubliceerd: Acta Neurochir (Wien). 2023;165(3):701-9.
Impact factor: 2.4 ; Q2

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10. Noninferiority of Posterior Cervical Foraminotomy vs Anterior Cervical Discectomy With Fusion for Procedural Success and Reduction in Arm Pain Among Patients With Cervical Radiculopathy at 1 Year: The FACET Randomized Clinical Trial
Broekema AEH, Simões de Souza NF, Soer R, Koopmans J, van Santbrink H, Arts MP, Burhani B, Bartels R, van der Gaag NA, Verhagen MHP, Tamási K, van Dijk JMC, Reneman MF, Groen RJM, Kuijlen JMA, FACET investigators: Hoss N.

mportance: The choice between posterior cervical foraminotomy (posterior surgery) and anterior cervical discectomy with fusion (anterior surgery) for cervical foraminal radiculopathy remains controversial.
Objective: To investigate the noninferiority of posterior vs anterior surgery in patients with cervical foraminal radiculopathy with regard to clinical outcomes after 1 year.
Design, setting, and participants: This multicenter investigator-blinded noninferiority randomized clinical trial was conducted from January 2016 to May 2020 with a total follow-up of 2 years. Patients were included from 9 hospitals in the Netherlands. Of 389 adult patients with 1-sided single-level cervical foraminal radiculopathy screened for eligibility, 124 declined to participate or did not meet eligibility criteria. Patients with pure axial neck pain without radicular pain were not eligible. Of 265 patients randomized (132 to posterior and 133 to anterior), 15 were lost to follow-up and 228 were included in the 1-year analysis (110 in posterior and 118 in anterior).
Interventions: Patients were randomly assigned 1:1 to posterior foraminotomy or anterior cervical discectomy with fusion.
Main outcomes and measures: Primary outcomes were proportion of success using Odom criteria and decrease in arm pain using a visual analogue scale from 0 to 100 with a noninferiority margin of 10% (assuming advantages with posterior surgery over anterior surgery that would justify a tolerable loss of efficacy of 10%). Secondary outcomes were neck pain, disability, quality of life, work status, treatment satisfaction, reoperations, and complications. Analyses were performed with 2-proportion z tests at 1-sided .05 significance levels with Bonferroni corrections.
Results: Among 265 included patients, the mean (SD) age was 51.2 (8.3) years; 133 patients (50%) were female and 132 (50%) were male. Patients were randomly assigned to posterior (132) or anterior (133) surgery. The proportion of success was 0.88 (86 of 98) in the posterior surgery group and 0.76 (81 of 106) in the anterior surgery group (difference, -0.11 percentage points; 1-sided 95% CI, -0.01) and the between-group difference in arm pain was -2.8 (1-sided 95% CI, -9.4) at 1-year follow-up, indicating noninferiority of posterior surgery. Decrease in arm pain had a between-group difference of 3.4 (1-sided 95% CI, 11.8), crossing the noninferiority margin with 1.8 points. All secondary outcomes had 2-sided 95% CIs clustered around 0 with small between-group differences.
Conclusions and relevance: In this randomized clinical trial, posterior surgery was noninferior to anterior surgery for patients with cervical radiculopathy regarding success rate and arm pain at 1

year. Decrease in arm pain and secondary outcomes had small between-group differences. These results may be used to enhance shared decision-making.

Gepubliceerd: JAMA Neurol. 2023;80(1):40-8.
Impact factor: 29.0 ; Q1

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11. Endovascular treatment for isolated posterior cerebral artery occlusion stroke in the MR CLEAN registry
Brouwer J, Ergezen S, Mulder M, Lycklama ANGJ, van Es A, van der Lugt A, Dippel DWJ, Majoie C, Roos Y, Coutinho JM, Emmer BJ, MR CLEAN Registry investigators: Brouwers P, Bulut T.

Background: Endovascular treatment (EVT) is standard of care in anterior circulation large vessel occlusions. In posterior circulation occlusions, data on EVT in isolated posterior cerebral artery (PCA) occlusions are limited, although PCA occlusions can cause severe neurological deficit.
Objective: To describe in a prospective study the clinical manifestations, outcomes, and safety of EVT in isolated PCA occlusions.
Methods: We used data (2014-2017) from the MR CLEAN Registry, a nationwide, prospective cohort of EVT-treated patients in the Netherlands. We included patients with acute ischemic stroke (AIS) due to an isolated PCA occlusion on CT angiography. Patients with concurrent occlusion of the basilar artery were excluded. Outcomes included change in National Institutes of Health Stroke Scale (ΔNIHSS) score, modified Rankin Scale (mRS) score 0-3 after 90 days, mortality, expanded Thrombolysis in Cerebral Infarction (eTICI), and periprocedural complications.
Results: Twenty (12%) of 162 patients with posterior circulation occlusions had an isolated PCA occlusion. Median age was 72 years; 13 (65%) were women. Median baseline NIHSS score was 13 (IQR 5-21). Six (30%) patients were comatose. Twelve patients (60%) received IVT. Median ΔNIHSS was -4 (IQR -11-+1). At follow-up, nine patients (45%) had mRS score 0-3. Seven (35%) died. eTICI 2b-3 was achieved in 13 patients (65%). Nine patients (45%) had periprocedural complications. No symptomatic intracranial hemorrhages (sICH) occurred.
Conclusions: EVT should be considered in selected patients with AIS with an isolated PCA occlusion, presenting with moderate-severe neurological deficits, as EVT was technically feasible in most of our patients and about half had good clinical outcome. In case of lower NIHSS score, a more conservative approach seems warranted, since periprocedural complications are not uncommon. Nonetheless, EVT seems reasonably safe considering the absence of sICH in our study.

Gepubliceerd: J Neurointerv Surg. 2023;15(4):363-9.
Impact factor: 4.9 ; Q1

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12. Successful reperfusion in relation to the number of passes: comparing outcomes of first pass expanded Treatment In Cerebral Ischemia (eTICI) 2B with multiple-pass eTICI 3
Bruggeman AAE, Kappelhof M, den Hartog SJ, Burke JF, Berkhemer OA, van Es A, van Zwam WH, Dippel DWJ, Coutinho JM, Marquering HA, Majoie C, Emmer BJ, MR CLEAN Registry investigators: Brouwers P, Bulut T.

Background: Higher expanded Treatment In Cerebral Ischemia (eTICI) reperfusion scores after endovascular treatment (EVT) are associated with better outcomes. However, the influence of the number of passes on this association is unclear. We aimed to compare outcomes of single-pass good reperfusion (eTICI 2B) with multiple-pass excellent/complete reperfusion (eTICI 2C/3) in daily clinical practice.

Methods: We compared outcomes of patients in the MR CLEAN Registry with good reperfusion (eTICI 2B) in a single pass to those with excellent/complete reperfusion (eTICI 2C/3) in multiple passes. Regression models were used to investigate the association of single-pass eTICI 2B versus multiple-pass eTICI 2C/3 reperfusion with 90-day functional outcome (modified Rankin Scale (mRS)), functional independence (mRS 0-2), per-procedural complications and safety outcomes.
Results: We included 699 patients: 178 patients with single-pass eTICI 2B, and 242 and 279 patients with eTICI 2C/3 after 2 and ≥3 passes, respectively. Patients with eTICI 2C/3 after 2 or ≥3 passes did not achieve significantly better functional outcomes compared with patients with single-pass eTICI 2B (adjusted common OR (acOR) 1.06, 95% CI 0.75 to 1.50 and acOR 0.88, 95% CI 0.74 to 1.05 for 90-day mRS, and adjusted OR (aOR) 1.24, 95% CI 0.78 to 1.97 and aOR 0.79, 95% CI 0.52 to 1.22 for functional independence).
Conclusions: Our results did not show better outcomes for patients who achieved eTICI 2C/3 in multiple, that is, two or more, passes when compared with patients with single-pass eTICI 2B. However, this concerns observational data. Further research is necessary to investigate the per-pass effect in relation to reperfusion and functional outcome.

Gepubliceerd: J Neurointerv Surg. 2023;15(2):120-6.
Impact factor: 4.9 ; Q1

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13. Development and Validation of a Postprocedural Model to Predict Outcome After Endovascular Treatment for Ischemic Stroke
Chalos V, Venema E, Mulder M, Roozenbeek B, Steyerberg EW, Wermer MJH, Lycklama À Nijeholt GJ, van der Worp HB, Goyal M, Campbell BCV, Muir KW, Guillemin F, Bracard S, White P, Dávalos A, Jovin TG, Hill MD, Mitchell PJ, Demchuk AM, Saver JL, van der Lugt A, Brown S, Dippel DWJ, Lingsma HF, MR CLEAN Registry Investigators: Brouwers P, Bulut T.

Importance: Outcome prediction after endovascular treatment (EVT) for ischemic stroke is important to patients, family members, and physicians.
Objective: To develop and validate a model based on preprocedural and postprocedural characteristics to predict functional outcome for individual patients after EVT.
Design, setting, and participants: A prediction model was developed using individual patient data from 7 randomized clinical trials, performed between December 2010 and December 2014. The model was developed within the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration and external validation in data from the Dutch Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry of patients treated in clinical practice between March 2014 and November 2017. Participants included patients from multiple centers throughout different countries in Europe, North America, East Asia, and Oceania (derivation cohort), and multiple centers in the Netherlands (validation cohort). Included were adult patients with a history of ischemic stroke from an intracranial large vessel occlusion in the anterior circulation who underwent EVT within 12 hours of symptom onset or last seen well. Data were last analyzed in July 2022.
Main outcome(s) and measure(s): A total of 19 variables were assessed by multivariable ordinal regression to predict functional outcome (modified Rankin Scale [mRS] score) 90 days after EVT. Variables were routinely available 1 day after EVT. Akaike information criterion (AIC) was used to optimize model fit vs model complexity. Probabilities for functional independence (mRS 0-2) and survival (mRS 0-5) were derived from the ordinal model. Model performance was expressed with discrimination (C statistic) and calibration.
Results: A total of 781 patients (median [IQR] age, 67 [57-76] years; 414 men [53%]) constituted the derivation cohort, and 3260 patients (median [IQR] age, 72 [61-80] years; 1684 men [52%]) composed the validation cohort. Nine variables were included in the model: age, baseline National Institutes of Health Stroke Scale (NIHSS) score, prestroke mRS score, history of diabetes, occlusion

location, collateral score, reperfusion grade, NIHSS score at 24 hours, and symptomatic intracranial hemorrhage 24 hours after EVT. External validation in the MR CLEAN Registry showed excellent discriminative ability for functional independence (C statistic, 0.91; 95% CI, 0.90-0.92) and survival (0.89; 95% CI, 0.88-0.90). The proportion of functional independence in the MR CLEAN Registry was systematically higher than predicted by the model (41% vs 34%), whereas observed and predicted survival were similar (72% vs 75%). The model was updated and implemented for clinical use.
Conclusion and relevance: The prognostic tool MR PREDICTS@24H can be applied 1 day after EVT to accurately predict functional outcome for individual patients at 90 days and to provide reliable outcome expectations and personalize follow-up and rehabilitation plans. It will need further validation and updating for contemporary patients.

Gepubliceerd: JAMA Neurol. 2023;80(9):940-8.
Impact factor: 29.0 ; Q1

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14. Ultrafast review of ambulatory EEGs with deep learning
da Silva Lourenço C, Tjepkema-Cloostermans MC, van Putten M.

Objective: Interictal epileptiform discharges (IED) are hallmark biomarkers of epilepsy which are typically detected through visual analysis. Deep learning has shown potential in automating IED detection, which could reduce the burden of visual analysis in clinical practice. This is particularly relevant for ambulatory electroencephalograms (EEGs), as these entail longer review times.
Methods: We applied a previously trained neural network to an independent dataset of 100 ambulatory EEGs (average duration 20.6 h). From these, 42 EEGs contained IEDs, 25 were abnormal without IEDs and 33 were normal. The algorithm flagged 2 second epochs that it considered IEDs. The EEGs were provided to an expert, who used NeuroCenter EEG to review the recordings. The expert concluded if each recording contained IEDs, and was timed during the process.
Results: The conclusion of the reviewer was the same as the EEG report in 97% of the recordings. Three EEGs contained IEDs that were not detected based on the flagged epochs. Review time for the 100 EEGs was approximately 4 h, with half of the recordings taking <2 minutes to review.
Conclusions: Our network can be used to reduce time spent on visual analysis in the clinic by 50-75 times with high reliability.
Significance: Given the large time reduction potential and high success rate, this algorithm can be used in the clinic to aid in visual analysis.

Gepubliceerd: Clin Neurophysiol. 2023;154:43-8.
Impact factor: 4.7 ; Q1

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15. Primary central nervous system lymphoma
de Koning ME, Hof JJ, Jansen C, Doorduijn JK, Bromberg JEC, van der Meulen M.

Primary central nervous system lymphoma (PCNSL) is a rare type of non-Hodgkin lymphoma (NHL) manifesting in the brain, spinal cord, cerebrospinal fluid and/or eyes, in the absence of systemic manifestations. With an increasing incidence and a 30% 5-year overall survival if promptly treated, timely diagnosis and subsequent treatment is paramount. The typical MRI appearance for PCNSL is a solitary or multiple T2-hypointense, homogeneous gadolinium-enhancing lesion with restricted diffusion. Dexamethasone treatment might compromise and delay the diagnosis. Hallmark of treatment is induction with intravenous high-dose methotrexate consisting polychemotherapy followed by consolidation treatment. Consolidation treatment consists of either whole brain

radiotherapy (WBRT) or autologous stem cell transplantation (ASCT). Given the (cognitive) side effects of WBRT, ASCT is increasingly being used as the first choice of treatment.

Gepubliceerd: J Neurol. 2023.
Impact factor: 6.0 ; Q1

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16. An in silico and in vitro human neuronal network model reveals cellular mechanisms beyond Na(V)1.1 underlying Dravet syndrome
Doorn N, van Hugte EJH, Ciptasari U, Mordelt A, Meijer HGE, Schubert D, Frega M, Nadif Kasri N, van Putten M.

Human induced pluripotent stem cell (hiPSC)-derived neuronal networks on multi-electrode arrays (MEAs) provide a unique phenotyping tool to study neurological disorders. However, it is difficult to infer cellular mechanisms underlying these phenotypes. Computational modeling can utilize the rich dataset generated by MEAs, and advance understanding of disease mechanisms. However, existing models lack biophysical detail, or validation and calibration to relevant experimental data. We developed a biophysical in silico model that accurately simulates healthy neuronal networks on MEAs. To demonstrate the potential of our model, we studied neuronal networks derived from a Dravet syndrome (DS) patient with a missense mutation in SCN1A, encoding sodium channel Na(V)1.1. Our in silico model revealed that sodium channel dysfunctions were insufficient to replicate the in vitro DS phenotype, and predicted decreased slow afterhyperpolarization and synaptic strengths. We verified these changes in DS patient-derived neurons, demonstrating the utility of our in silico model to predict disease mechanisms.

Gepubliceerd: Stem Cell Reports. 2023;18(8):1686-700.
Impact factor: 5.9 ; Q2

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17. Trigger Factors for Stroke in Young Adults: A Case-Crossover Study
Ekker MS, Verhoeven JI, Rensink KML, Schellekens MMI, Boot EM, van Alebeek ME, Brouwers P, Arntz RM, van Dijk GW, Gons RAR, van Uden IWM, den Heijer T, de Kort PLM, de Laat KF, van Norden AGW, Vermeer SE, van Zagten M, van Oostenbrugge RJ, Wermer MJH, Nederkoorn PJ, Kerkhoff H, Rooyer F, van Rooij FG, van den Wijngaard IR, Klijn CJM, Tuladhar AM, de Leeuw FE.

Background and objectives: Causes of stroke in young adults differ from those in the elderly individuals, and in a larger percentage, no cause can be determined. To gain more insight into the etiology of (cryptogenic) stroke in the young population, we investigated whether trigger factors, such as short-lasting exposure to toxins or infection, may play a role.
Methods: Patients aged 18-49 years with a first-ever ischemic stroke or intracerebral hemorrhage (ICH) in 17 participating centers in the Netherlands completed a questionnaire about exposure to 9 potential trigger factors in hazard periods and on a regular yearly basis. A case-crossover design was used to assess relative risks (RRs) with 95% confidence intervals (95% CIs) by the Mantel-Haenszel case-crossover method, for any stroke (ischemic stroke and ICH combined) and for different etiologic subgroups of ischemic stroke.
Results: One thousand one hundred forty-six patients completed the questionnaire (1,043 patients with an ischemic stroke and 103 with an ICH, median age 44.0 years, 52.6% men). For any stroke, an increased risk emerged within 1 hour of cola consumption (RR 2.0, 95% CI 1.5-2.8) and vigorous physical exercise (RR 2.6, 95% CI 2.2-3.0), within 2 hours after sexual activity (RR 2.4, 95% CI 1.6-3.5), within 4 hours after illicit drug use (RR 2.8, 95% CI 1.7-4.9), and within 24 hours after fever or flu-like disease (RR 14.1, 95% CI 10.5-31.2; RR 13.9, 95% CI 8.9-21.9). Four trigger factors increased the risk

of other determined and cryptogenic ischemic stroke, 3 that of cardioembolic stroke, 2 that of large vessel atherosclerosis and likely atherothrombotic stroke combined and stroke with multiple causes, and none that of stroke due to small vessel disease.
Discussion: We identified cola consumption, vigorous physical exercise, sexual activity, illicit drug use, fever, and flu-like disease as potential trigger factors for stroke in the young population and found differences in the type and number of trigger factors associated with different etiologic subgroups of ischemic stroke. These findings might help in better understanding the pathophysiologic mechanisms of (cryptogenic) stroke in the young population.

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Impact factor: 10.1 ; Q1

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18. Risk Factors and Causes of Ischemic Stroke in 1322 Young Adults
Ekker MS, Verhoeven JI, Schellekens MMI, Boot EM, van Alebeek ME, Brouwers P, Arntz RM, van Dijk GW, Gons RAR, van Uden IWM, den Heijer T, de Kort PLM, de Laat KF, van Norden AGW, Vermeer SE, van Zagten MSG, van Oostenbrugge RJ, Wermer MJH, Nederkoorn PJ, Zonneveld TP, Kerkhoff H, Rooyer FA, van Rooij FG, van den Wijngaard IR, Klijn CJM, Tuladhar AM, de Leeuw FE.

Background: Identification of risk factors and causes of stroke is key to optimize treatment and prevent recurrence. Up to one-third of young patients with stroke have a cryptogenic stroke according to current classification systems (Trial of ORG 10172 in Acute Stroke Treatment [TOAST] and atherosclerosis, small vessel disease, cardiac pathology, other causes, dissection [ASCOD]). The aim was to identify risk factors and leads for (new) causes of cryptogenic ischemic stroke in young adults, using the pediatric classification system from the IPSS study (International Pediatric Stroke Study).
Methods: This is a multicenter prospective cohort study conducted in 17 hospitals in the Netherlands, consisting of 1322 patients aged 18 to 49 years with first-ever, imaging confirmed, ischemic stroke between 2013 and 2021. The main outcome was distribution of risk factors according to IPSS classification in patients with cryptogenic and noncryptogenic stroke according to the TOAST and ASCOD classification.
Results: The median age was 44.2 years, and 697 (52.7%) were men. Of these 1322 patients, 333 (25.2%) had a cryptogenic stroke according to the TOAST classification. Additional classification using the ASCOD criteria reduced the number patients with cryptogenic stroke from 333 to 260 (19.7%). When risk factors according to the IPSS were taken into account, the number of patients with no potential cause or risk factor for stroke reduced to 10 (0.8%).
Conclusions: Among young adults aged 18 to 49 years with a cryptogenic ischemic stroke according to the TOAST classification, risk factors for stroke are highly prevalent. Using a pediatric classification system provides new leads for the possible causes in cryptogenic stroke, and could potentially lead to more tailored treatment for young individuals with stroke.

Gepubliceerd: Stroke. 2023;54(2):439-47.
Impact factor: 8.4 ; Q1

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19. Levodopa Response in Patients With Early Parkinson Disease: Further Observations of the LEAP Study
Frequin HL, Schouten J, Verschuur CVM, Suwijn SR, Boel JA, Post B, Bloem BR, van Hilten JJ, van Laar T, Tissingh G, Munts AG, Dijk JM, Deuschl G, Lang A, Dijkgraaf MGW, de Haan RJ, de Bie RMA, LEAP Study Group: Dorresteijn LDA.

Background and objectives: The Levodopa in EArly Parkinson's Disease (LEAP) study enabled us to conduct post hoc analyses concerning the effects of levodopa in patients with early Parkinson disease.
Methods: The LEAP study was a double-blind, placebo-controlled, randomized, delayed-start trial in which patients with early Parkinson disease were randomized to receive levodopa/carbidopa 300/75 mg daily for 80 weeks (early-start group) or to placebo for 40 weeks followed by levodopa/carbidopa 300/75 mg daily for 40 weeks (delayed-start group). We analyzed the effect of levodopa with the Unified Parkinson's Disease Rating Scale on bradykinesia, rigidity, and tremor. At week 80, participants answered 3 questions regarding motor response fluctuations.
Results: A total of 222 patients were randomized to the early-start group (mean ± SD age at baseline 64.8 ± 8.7 years; 71% male) and 223 to the delayed-start group (mean ± SD age at baseline 65.5 ± 8.8 years; 69% male). The difference between the early- and delayed-start groups in mean change from baseline to week 4, expressed as Hedges *g* effect size, was -0.33 for bradykinesia, -0.29 for rigidity, and -0.25 for tremor (for all symptoms indicating a small effect in favor of the early-start group); from baseline to week 22, respectively, -0.49, -0.36, and -0.44 (small to medium effect); and from baseline to week 40, respectively, -0.32, -0.19, and -0.27 (small effect). At 80 weeks, fewer patients in the early-start group (46 of 205 patients, 23%) experienced motor response fluctuations than patients in the delayed-start group (81 of 211, 38%; $p < 0.01$).
Discussion: In patients with early Parkinson disease, levodopa improves bradykinesia, rigidity, and tremor to the same order of magnitude. For all 3 symptoms, effects were larger at 22 weeks compared with 4 weeks. At 80 weeks, there were fewer patients with motor response fluctuations in the group that had started levodopa earlier.
Classification of evidence: This study provides Class II evidence that the effect of levodopa on bradykinesia, rigidity, and tremor is larger after 22 weeks compared with 4 weeks of treatment.

Gepubliceerd: Neurology. 2023;100(4):e367-e76.
Impact factor: 10.1 ; Q1

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20. Predicting Motor Outcome and Quality of Life After Subthalamic Deep Brain Stimulation for Parkinson's Disease: The Role of Standard Screening Measures and Wearable-Data
Geraedts VJ, van Vugt JPP, Marinus J, Kuiper R, Middelkoop HAM, Zutt R, van der Gaag NA, Hoffmann CFE, Dorresteijn LDA, van Hilten JJ, Contarino MF.

Background: Standardized screening for subthalamic deep brain stimulation (STN DBS) in Parkinson's disease (PD) patients is crucial to determine eligibility, but its utility to predict postoperative outcomes in eligible patients is inconclusive. It is unknown whether wearable data can contribute to this aim.
Objective: To evaluate the utility of universal components incorporated in the DBS screening, complemented by a wearable sensor, to predict motor outcomes and Quality of life (QoL) one year after STN DBS surgery.
Methods: Consecutive patients were included in the OPTIMIST cohort study from two DBS centers. Standardized assessments included a preoperative Levodopa Challenge Test (LCT), and questionnaires on QoL and non-motor symptoms including cognition, psychiatric symptoms, impulsiveness, autonomic symptoms, and sleeping problems. Moreover, an ambulatory wearable sensor (Parkinson Kinetigraph (PKG)) was used. Postoperative assessments were similar and also included a Stimulation Challenge Test to determine DBS effects on motor function.
Results: Eighty-three patients were included (median (interquartile range) age 63 (56-68) years, 36% female). Med-OFF (Stim-OFF) motor severity deteriorated indicating disease progression, but patients significantly improved in terms of Med-ON (Stim-ON) motor function, motor fluctuations, QoL, and most non-motor domains. Motor outcomes were not predicted by preoperative tests, including

covariates of either LCT or PKG. Postoperative QoL was predicted by better preoperative QoL, lower age, and more preoperative impulsiveness scores in multivariate models.
Conclusion: Data from the DBS screening including wearable data do not predict postoperative motor outcome at one year. Post-DBS QoL appears primarily driven by non-motor symptoms, rather than by motor improvement.

Gepubliceerd: J Parkinsons Dis. 2023;13(4):575-88.
Impact factor: 5.2 ; Q1

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21. Association between thrombus composition and stroke etiology in the MR CLEAN Registry biobank
Hund HM, Boodt N, Hansen D, Haffmans WA, Lycklama À Nijeholt GJ, Hofmeijer J, Dippel DWJ, van der Lugt A, van Es A, van Beusekom HMM, MR CLEAN Registry Investigators: Brouwers P, Bulut T.

Purpose: The composition of thrombi retrieved during endovascular thrombectomy (EVT) in acute ischemic stroke (AIS) due to large vessel occlusion (LVO) may differ depending on their origin. In this study, we investigated the association between thrombus composition and stroke etiology in a large population of patients from the Dutch MR CLEAN Registry treated with EVT in daily clinical practice.
Methods: The thrombi of 332 patients with AIS were histologically analyzed for red blood cells (RBC), fibrin/platelets (F/P), and white blood cells (leukocytes) using a machine learning algorithm. Stroke etiology was assessed using the Trial of Org 10,172 in acute stroke treatment (TOAST) classification.
Results: The thrombi of cardioembolic origin contained less RBC and more F/P than those of non-cardioembolic origin (25.8% vs 41.2% RBC [p = 0.003] and 67.1% vs 54.5% F/P [p = 0.004]). The likelihood of a non-cardioembolic source of stroke increased with increasing thrombus RBC content (OR 1.02; [95% CI 1.00-1.06] for each percent increase) and decreased with a higher F/P content (OR 1.02; [95% CI 1.00-1.06]). Thrombus composition in patients with a cardioembolic origin and undetermined origin was similar.
Conclusion: Thrombus composition is significantly associated with stroke etiology, with an increase in RBC and a decrease in F/P raising the odds for a non-cardioembolic cause. No difference between composition of cardioembolic thrombi and of undetermined origin was seen. This emphasizes the need for more extensive monitoring for arrhythmias and/or extended cardiac analysis in case of an undetermined origin.

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Impact factor: 2.8 ; Q3

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22. Comparison of state-of-the-art deep learning architectures for detection of freezing of gait in Parkinson's disease
Klaver EC, Heijink IB, Silvestri G, van Vugt JPP, Janssen S, Nonnekes J, van Wezel RJA, Tjepkema-Cloostermans MC.

Introduction: Freezing of gait (FOG) is one of the most debilitating motor symptoms experienced by patients with Parkinson's disease (PD). FOG detection is possible using acceleration data from wearable sensors, and a convolutional neural network (CNN) is often used to determine the presence of FOG epochs. We compared the performance of a standard CNN for the detection of FOG with two more complex networks, which are well suited for time series data, the MiniRocket and the InceptionTime.
Methods: We combined acceleration data of people with PD across four studies. The final data set was split into a training (80%) and hold-out test (20%) set. A fifth study was included as an unseen

test set. The data were windowed (2 s) and five-fold cross-validation was applied. The CNN, MiniRocket, and InceptionTime models were evaluated using a receiver operating characteristic (ROC) curve and its area under the curve (AUC). Multiple sensor configurations were evaluated for the best model. The geometric mean was subsequently calculated to select the optimal threshold. The selected model and threshold were evaluated on the hold-out and unseen test set.
Results: A total of 70 participants (23.7 h, 9% FOG) were included in this study for training and testing, and in addition, 10 participants provided an unseen test set (2.4 h, 11% FOG). The CNN performed best (AUC = 0.86) in comparison to the InceptionTime (AUC = 0.82) and MiniRocket (AUC = 0.76) models. For the CNN, we found a similar performance for a seven-sensor configuration (lumbar, upper and lower legs and feet; AUC = 0.86), six-sensor configuration (upper and lower legs and feet; AUC = 0.87), and two-sensor configuration (lower legs; AUC = 0.86). The optimal threshold of 0.45 resulted in a sensitivity of 77% and a specificity of 58% for the hold-out set (AUC = 0.72), and a sensitivity of 85% and a specificity of 68% for the unseen test set (AUC = 0.90).
Conclusion: We confirmed that deep learning can be used to detect FOG in a large, heterogeneous dataset. The CNN model outperformed more complex networks. This model could be employed in future personalized interventions, with the ultimate goal of using automated FOG detection to trigger real-time cues to alleviate FOG in daily life.

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Impact factor: 3.4 ; Q2

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23. Good vibrations: tactile cueing for freezing of gait in Parkinson's disease
Klaver EC, van Vugt JPP, Bloem BR, van Wezel RJA, Nonnekes J, Tjepkema-Cloostermans MC.

Background: Cueing strategies can alleviate freezing of gait (FOG) in people with Parkinson's disease (PD). We evaluated tactile cueing delivered via vibrating socks, which has the benefit of not being noticeable to bystanders.
Objective: To evaluate the effect of tactile cueing compared to auditory cueing on FOG.
Methods: Thirty-one persons with PD with FOG performed gait tasks during both ON and OFF state. The effect of open loop and closed loop tactile cueing, as delivered by vibrating socks, was compared to an active control group (auditory cueing) and to a baseline condition (uncued gait). These four conditions were balanced between subjects. Gait tasks were videotaped and annotated for FOG by two experienced raters. Motion data were collected to analyze spatiotemporal gait parameters. Responders were defined as manifesting a relative reduction of > 10% in the percent time frozen compared to uncued gait.
Results: The average percent time frozen during uncued gait was 11.2% in ON and 21.5% in OFF state. None of the three tested cueing modalities affected the percentage of time frozen in either the ON ($p = 0.20$) or OFF state ($p = 0.12$). The number of FOG episodes and spatiotemporal gait parameters were also not affected. We found that 22 out of 31 subjects responded to cueing, the response to the three types of cueing was highly individual.
Conclusions: Cueing did not improve FOG at the group level; however, tactile as well as auditory cueing improved FOG in many individuals. This highlights the need for a personalized approach when using cueing to treat FOG.

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Impact factor: 6.0 ; Q1

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24. Prediction in cultured cortical neural networks
Lamberti M, Tripathi S, van Putten M, Marzen S, le Feber J.

Theory suggest that networks of neurons may predict their input. Prediction may underlie most aspects of information processing and is believed to be involved in motor and cognitive control and decision-making. Retinal cells have been shown to be capable of predicting visual stimuli, and there is some evidence for prediction of input in the visual cortex and hippocampus. However, there is no proof that the ability to predict is a generic feature of neural networks. We investigated whether random in vitro neuronal networks can predict stimulation, and how prediction is related to short- and long-term memory. To answer these questions, we applied two different stimulation modalities. Focal electrical stimulation has been shown to induce long-term memory traces, whereas global optogenetic stimulation did not. We used mutual information to quantify how much activity recorded from these networks reduces the uncertainty of upcoming stimuli (prediction) or recent past stimuli (short-term memory). Cortical neural networks did predict future stimuli, with the majority of all predictive information provided by the immediate network response to the stimulus. Interestingly, prediction strongly depended on short-term memory of recent sensory inputs during focal as well as global stimulation. However, prediction required less short-term memory during focal stimulation. Furthermore, the dependency on short-term memory decreased during 20 h of focal stimulation, when long-term connectivity changes were induced. These changes are fundamental for long-term memory formation, suggesting that besides short-term memory the formation of long-term memory traces may play a role in efficient prediction.

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Impact factor: onbekend

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25. Spatiotemporal spike-centered averaging reveals symmetry of temporal and spatial components of the spike-LFP relationship during human focal seizures

Lee S, Deshpande SS, Merricks EM, Schlafly E, Goodman R, McKhann GM, Eskandar EN, Madsen JR, Cash SS, van Putten M, Schevon CA, van Drongelen W.

The electrographic manifestation of neural activity can reflect the relationship between the faster action potentials of individual neurons and the slower fluctuations of the local field potential (LFP). This relationship is typically examined in the temporal domain using the spike-triggered average. In this study, we add a spatial component to this relationship. Here we first derive a theoretical model of the spike-LFP relationship across a macroelectrode. This mathematical derivation showed a special symmetry in the spike-LFP relationship wherein a sinc function in the temporal domain predicts a sinc function in the spatial domain. We show that this theoretical result is observed in a real-world system by characterizing the spike-LFP relationship using microelectrode array (MEA) recordings of human focal seizures. To do this, we present a approach, termed the spatiotemporal spike-centered average (st-SCA), that allows for visualization of the spike-LFP relationship in both the temporal and spatial domains. We applied this method to 25 MEA recordings obtained from seven patients with pharmacoresistant focal epilepsy. Of the five patients with MEAs implanted in recruited territory, three exhibited spatiotemporal patterns consistent with a sinc function, and two exhibited spatiotemporal patterns resembling deep wells of excitation. These results suggest that in some cases characterization of the spike-LFP relationship in the temporal domain is sufficient to predict the underlying spatial pattern. Finally, we discuss the biological interpretation of these findings and propose that the sinc function may reflect the role of mid-range excitatory connections during seizure activity.

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Impact factor: 5.9 ; Q1

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26. Dexamethasone versus Surgery for Chronic Subdural Hematoma
Miah IP, Holl DC, Blaauw J, Lingsma HF, den Hertog HM, Jacobs B, Kruyt ND, van der Naalt J, Polinder S, Groen RJM, Kho KH, van Kooten F, Dirven CMF, Peul WC, Jellema K, Dammers R, van der Gaag NA.

Background: The role of glucocorticoids without surgical evacuation in the treatment of chronic subdural hematoma is unclear.
Methods: In this multicenter, open-label, controlled, noninferiority trial, we randomly assigned symptomatic patients with chronic subdural hematoma in a 1:1 ratio to a 19-day tapering course of dexamethasone or to burr-hole drainage. The primary end point was the functional outcome at 3 months after randomization, as assessed by the score on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]). Noninferiority was defined by a lower limit of the 95% confidence interval of the odds ratio for a better functional outcome with dexamethasone than with surgery of 0.9 or more. Secondary end points included scores on the Markwalder Grading Scale of symptom severity and on the Extended Glasgow Outcome Scale.
Results: From September 2016 through February 2021, we enrolled 252 patients of a planned sample size of 420; 127 were assigned to the dexamethasone group and 125 to the surgery group. The mean age of the patients was 74 years, and 77% were men. The trial was terminated early by the data and safety monitoring board owing to safety and outcome concerns in the dexamethasone group. The adjusted common odds ratio for a lower (better) score on the modified Rankin scale at 3 months with dexamethasone than with surgery was 0.55 (95% confidence interval, 0.34 to 0.90), which failed to show noninferiority of dexamethasone. The scores on the Markwalder Grading Scale and Extended Glasgow Outcome Scale were generally supportive of the results of the primary analysis. Complications occurred in 59% of the patients in the dexamethasone group and 32% of those in the surgery group, and additional surgery was performed in 55% and 6%, respectively.
Conclusions: In a trial that involved patients with chronic subdural hematoma and that was stopped early, dexamethasone treatment was not found to be noninferior to burr-hole drainage with respect to functional outcomes and was associated with more complications and a greater likelihood of later surgery. (Funded by the Netherlands Organization for Health Research and Development and others; DECSA EudraCT number, 2015-001563-39.).

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Impact factor: 158.5 ; Q1

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27. Myoclonus in comatose patients with electrographic status epilepticus after cardiac arrest: Corresponding EEG patterns, effects of treatment and outcomes
Nutma S, Ruijter BJ, Beishuizen A, Tromp SC, Scholten E, Horn J, van den Bergh WM, van Kranen-Mastenbroek VH, Thomeer EC, Moudrous W, Aries M, van Putten MJ, Hofmeijer J.

Objective: To clarify the significance of any form of myoclonus in comatose patients after cardiac arrest with rhythmic and periodic EEG patterns (RPPs) by analyzing associations between myoclonus and EEG pattern, response to anti-seizure medication and neurological outcome.
Design: Post hoc analysis of the prospective randomized Treatment of ELectroencephalographic STatus Epilepticus After Cardiopulmonary Resuscitation (TELSTAR) trial.
Setting: Eleven ICUs in the Netherlands and Belgium.
Patients: One hundred and fifty-seven adult comatose post-cardiac arrest patients with RPPs on continuous EEG monitoring.
Interventions: Anti-seizure medication vs no anti-seizure medication in addition to standard care.
Measurements and main results: Of 157 patients, 98 (63%) had myoclonus at inclusion. Myoclonus was not associated with one specific RPP type. However, myoclonus was associated with a smaller probability of a continuous EEG background pattern (48% in patients with vs 75% without myoclonus,

odds ratio (OR) 0.31; 95% confidence interval (CI) 0.16-0.64) and earlier onset of RPPs (24% vs 9% within 24 hours after cardiac arrest, OR 3.86;95% CI 1.64-9.11). Myoclonus was associated with poor outcome at three months, but not invariably so (poor neurological outcome in 96% vs 82%, p = 0.004). Anti-seizure medication did not improve outcome, regardless of myoclonus presence (6% good outcome in the intervention group vs 2% in the control group, OR 0.33; 95% CI 0.03-3.32).
Conclusions: Myoclonus in comatose patients after cardiac arrest with RPPs is associated with poor outcome and discontinuous or suppressed EEG. However, presence of myoclonus does not interact with the effects of anti-seizure medication and cannot predict a poor outcome without false positives.

Gepubliceerd: Resuscitation. 2023;186:109745.
Impact factor: 6.5 ; Q1

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28. Endovascular treatment versus no endovascular treatment after 6-24 h in patients with ischaemic stroke and collateral flow on CT angiography (MR CLEAN-LATE) in the Netherlands: a multicentre, open-label, blinded-endpoint, randomised, controlled, phase 3 trial
Olthuis SGH, Pirson FAV, Pinckaers FME, Hinsenveld WH, Nieboer D, Ceulemans A, Knapen R, Robbe MMQ, Berkhemer OA, van Walderveen MAA, Lycklama À Nijeholt GJ, Uyttenboogaart M, Schonewille WJ, van der Sluijs PM, Wolff L, van Voorst H, Postma AA, Roosendaal SD, van der Hoorn A, Emmer BJ, Krietemeijer MGM, van Doormaal PJ, Roozenbeek B, Goldhoorn RB, Staals J, de Ridder IR, van der Leij C, Coutinho JM, van der Worp HB, Lo RTH, Bokkers RPH, van Dijk EI, Boogaarts HD, Wermer MJH, van Es A, van Tuijl JH, Kortman HGJ, Gons RAR, Yo LSF, Vos JA, de Laat KF, van Dijk LC, van den Wijngaard IR, Hofmeijer J, Martens JM, Brouwers P, Bulut T, Remmers MJM, de Jong T, den Hertog HM, van Hasselt B, Rozeman AD, Elgersma OEH, van der Veen B, Sudiono DR, Lingsma HF, Roos Y, Majoie C, van der Lugt A, Dippel DWJ, van Zwam WH, van Oostenbrugge RJ.

Background: Endovascular treatment for anterior circulation ischaemic stroke is effective and safe within a 6 h window. MR CLEAN-LATE aimed to assess efficacy and safety of endovascular treatment for patients treated in the late window (6-24 h from symptom onset or last seen well) selected on the basis of the presence of collateral flow on CT angiography (CTA).
Methods: MR CLEAN-LATE was a multicentre, open-label, blinded-endpoint, randomised, controlled, phase 3 trial done in 18 stroke intervention centres in the Netherlands. Patients aged 18 years or older with ischaemic stroke, presenting in the late window with an anterior circulation large-vessel occlusion and collateral flow on CTA, and a neurological deficit score of at least 2 on the National Institutes of Health Stroke Scale were included. Patients who were eligible for late-window endovascular treatment were treated according to national guidelines (based on clinical and perfusion imaging criteria derived from the DAWN and DEFUSE-3 trials) and excluded from MR CLEAN-LATE enrolment. Patients were randomly assigned (1:1) to receive endovascular treatment or no endovascular treatment (control), in addition to best medical treatment. Randomisation was web based, with block sizes ranging from eight to 20, and stratified by centre. The primary outcome was the modified Rankin Scale (mRS) score at 90 days after randomisation. Safety outcomes included all-cause mortality at 90 days after randomisation and symptomatic intracranial haemorrhage. All randomly assigned patients who provided deferred consent or died before consent could be obtained comprised the modified intention-to-treat population, in which the primary and safety outcomes were assessed. Analyses were adjusted for predefined confounders. Treatment effect was estimated with ordinal logistic regression and reported as an adjusted common odds ratio (OR) with a 95% CI. This trial was registered with the ISRCTN, ISRCTN19922220.
Findings: Between Feb 2, 2018, and Jan 27, 2022, 535 patients were randomly assigned, and 502 (94%) patients provided deferred consent or died before consent was obtained (255 in the endovascular treatment group and 247 in the control group; 261 [52%] females). The median mRS score at 90 days was lower in the endovascular treatment group than in the control group (3 [IQR 2-5]

vs 4 [2-6]), and we observed a shift towards better outcomes on the mRS for the endovascular treatment group (adjusted common OR 1·67 [95% CI 1·20-2·32]). All-cause mortality did not differ significantly between groups (62 [24%] of 255 patients vs 74 [30%] of 247 patients; adjusted OR 0·72 [95% CI 0·44-1·18]). Symptomatic intracranial haemorrhage occurred more often in the endovascular treatment group than in the control group (17 [7%] vs four [2%]; adjusted OR 4·59 [95% CI 1·49-14·10]).
Interpretation: In this study, endovascular treatment was efficacious and safe for patients with ischaemic stroke caused by an anterior circulation large-vessel occlusion who presented 6-24 h from onset or last seen well, and who were selected on the basis of the presence of collateral flow on CTA. Selection of patients for endovascular treatment in the late window could be primarily based on the presence of collateral flow.
Funding: Collaboration for New Treatments of Acute Stroke consortium, Dutch Heart Foundation, Stryker, Medtronic, Cerenovus, Top Sector Life Sciences & Health, and the Netherlands Brain Foundation.

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Impact factor: 168.9 ; Q1

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29. Cost-utility analysis of a structured medication review compared to usual care in Parkinson's disease

Oonk NGM, Dorresteijn LDA, van den Berg AD, van der Palen J, Movig KLL, Nijmeijer HW, van Kesteren ME, Koffijberg H.

Purpose: For controlling symptoms in Parkinson's disease (PD) together with treating additional comorbidities, patients often face complex medication regimens, with suboptimal adherence, drug-related problems, and diminished therapy efficacy as a common consequence. A medication review could potentially tackle these issues, among others by optimizing drug treatment. Even if no change in clinical outcomes is observed, this intervention might decrease health care costs by reducing drug-related problems and hospital admissions. This study aimed to gain more insight in the health benefits and costs of a structured medication review (SMR) in PD.
Methods: A cost-utility analysis was performed, based on a multicenter randomized controlled trial with 202 PD patients with polypharmacy. The intervention group received an SMR, whereas the control group received usual care. The intervention effect after 6 months of follow-up was presented as incremental quality-adjusted life years (QALY) using the EQ-5D-5L questionnaire. Costs were based on real-world data. Missing data was imputed using multiple imputation techniques. Bootstrapping was used to estimate the uncertainty in all health and economic outcomes.
Results: The QALY gain in the intervention group compared to the control group was - 0.011 (95% CI - 0.043; 0.020). Incremental costs were €433 (95% CI - 873; 1687). When adapting a willingness-to-pay threshold of €20,000/QALY and €80,000/QALY, the probability of SMRs being cost-effective was 18% and 30%, respectively.
Conclusion: A community pharmacist-led SMR in PD patients in the current setting shows no apparent benefit and is not cost-effective after 6 months, compared to usual care.
Trial registration: Netherlands Trial Register, NL4360. Registered 17 March 2014.

Gepubliceerd: Eur J Clin Pharmacol. 2023;79(2):289-97.
Impact factor: 2.9 ; Q3

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30. Deep Brain Stimulation of the Anterior Nucleus of the Thalamus in Drug-Resistant Epilepsy in the MORE Multicenter Patient Registry

Peltola J, Colon AJ, Pimentel J, Coenen VA, Gil-Nagel A, Gonçalves Ferreira A, Lehtimäki K, Ryvlin P, Taylor RS, Ackermans L, Ardesch J, Bentes C, Bosak M, Burneo JG, Chamadoira C, Elger CE, Erőss L, Fabo D, Faulkner H, Gawlowicz J, Gharabaghi A, Iacoangeli M, Janszky J, Järvenpää S, Kaufmann E, Kho KH, Kumlien E, Laufs H, Lettieri C, Linhares P, Noachtar S, Parrent A, Pataraia E, Patel NK, Peralta AR, Rácz A, Campos AR, Rego R, Ricciuti RA, Rona S, Rouhl RPW, Schulze-Bonhage A, Schuurman R, Sprengers M, Sufianov A, Temel Y, Theys T, Van Paesschen W, Van Roost D, Vaz R, Vonck K, Wagner L, Zwemmer J, Abouihia A, Brionne TC, Gielen F, Boon P.

Background and objectives: The efficacy of deep brain stimulation of the anterior nucleus of the thalamus (ANT DBS) in patients with drug-resistant epilepsy (DRE) was demonstrated in the double-blind Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy randomized controlled trial. The Medtronic Registry for Epilepsy (MORE) aims to understand the safety and longer-term effectiveness of ANT DBS therapy in routine clinical practice.
Methods: MORE is an observational registry collecting prospective and retrospective clinical data. Participants were at least 18 years old, with focal DRE recruited across 25 centers from 13 countries. They were followed for at least 2 years in terms of seizure frequency (SF), responder rate (RR), health-related quality of life (Quality of Life in Epilepsy Inventory 31), depression, and safety outcomes.
Results: Of the 191 patients recruited, 170 (mean [SD] age of 35.6 [10.7] years, 43% female) were implanted with DBS therapy and met all eligibility criteria. At baseline, 38% of patients reported cognitive impairment. The median monthly SF decreased by 33.1% from 15.8 at baseline to 8.8 at 2 years ($p < 0.0001$) with 32.3% RR. In the subgroup of 47 patients who completed 5 years of follow-up, the median monthly SF decreased by 55.1% from 16 at baseline to 7.9 at 5 years ($p < 0.0001$) with 53.2% RR. High-volume centers (>10 implantations) had 42.8% reduction in median monthly SF by 2 years in comparison with 25.8% in low-volume center. In patients with cognitive impairment, the reduction in median monthly SF was 26.0% by 2 years compared with 36.1% in patients without cognitive impairment. The most frequently reported adverse events were changes (e.g., increased frequency/severity) in seizure (16%), memory impairment (patient-reported complaint, 15%), depressive mood (patient-reported complaint, 13%), and epilepsy (12%). One definite sudden unexpected death in epilepsy case was reported.
Discussion: The MORE registry supports the effectiveness and safety of ANT DBS therapy in a real-world setting in the 2 years following implantation.
Classification of evidence: This study provides Class IV evidence that ANT DBS reduces the frequency of seizures in patients with drug-resistant focal epilepsy.
Trial registration information: MORE ClinicalTrials.gov Identifier: NCT01521754, first posted on January 31, 2012.

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Impact factor: 10.1 ; Q1

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31. Patterns of oral anticoagulant use and outcomes in Asian patients with atrial fibrillation: a post-hoc analysis from the GLORIA-AF Registry

Romiti GF, Corica B, Proietti M, Mei DA, Frydenlund J, Bisson A, Boriani G, Olshansky B, Chan YH, Huisman MV, Chao TF, Lip GYH, GLORIA-AF Investigators: Brouwers P.

Background: Previous studies suggested potential ethnic differences in the management and outcomes of atrial fibrillation (AF). We aim to analyse oral anticoagulant (OAC) prescription, discontinuation, and risk of adverse outcomes in Asian patients with AF, using data from a global prospective cohort study.
Methods: From the GLORIA-AF Registry Phase II-III (November 2011-December 2014 for Phase II, and January 2014-December 2016 for Phase III), we analysed patients according to their self-reported ethnicity (Asian vs. non-Asian), as well as according to Asian subgroups (Chinese, Japanese, Korean

and other Asian). Logistic regression was used to analyse OAC prescription, while the risk of OAC discontinuation and adverse outcomes were analysed through Cox-regression model. Our primary outcome was the composite of all-cause death and major adverse cardiovascular events (MACE). The original studies were registered with ClinicalTrials.gov, NCT01468701, NCT01671007, and NCT01937377.
Findings: 34,421 patients were included (70.0 ± 10.5 years, 45.1% females, 6900 (20.0%) Asian: 3829 (55.5%) Chinese, 814 (11.8%) Japanese, 1964 (28.5%) Korean and 293 (4.2%) other Asian). Most of the Asian patients were recruited in Asia (n = 6701, 97.1%), while non-Asian patients were mainly recruited in Europe (n = 15,449, 56.1%) and North America (n = 8378, 30.4%). Compared to non-Asian individuals, prescription of OAC and non-vitamin K antagonist oral anticoagulant (NOAC) was lower in Asian patients (Odds Ratio [OR] and 95% Confidence Intervals (CI): 0.23 [0.22-0.25] and 0.66 [0.61-0.71], respectively), but higher in the Japanese subgroup. Asian ethnicity was also associated with higher risk of OAC discontinuation (Hazard Ratio [HR] and [95% CI]: 1.79 [1.67-1.92]), and lower risk of the primary composite outcome (HR [95% CI]: 0.86 [0.76-0.96]). Among the exploratory secondary outcomes, Asian ethnicity was associated with higher risks of thromboembolism and intracranial haemorrhage, and lower risk of major bleeding.
Interpretation: Our results showed that Asian patients with AF showed suboptimal thromboembolic risk management and a specific risk profile of adverse outcomes; these differences may also reflect differences in country-specific factors. Ensuring integrated and appropriate treatment of these patients is crucial to improve their prognosis.
Funding: The GLORIA-AF Registry was funded by Boehringer Ingelheim GmbH.

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Impact factor: 15.1 ; Q1

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32. Natural history, angiographic presentation and outcomes of anterior cranial fossa dural arteriovenous fistulas

Sanchez S, Raghuram A, Wendt L, Hayakawa M, Chen CJ, Sheehan JP, Kim LJ, Abecassis IJ, Levitt MR, Meyer RM, Guniganti R, Kansagra AP, Lanzino G, Giordan E, Brinjikji W, Bulters DO, Durnford A, Fox WC, Smith J, Polifka AJ, Gross B, Amin-Hanjani S, Alaraj A, Kwasnicki A, Starke RM, Chen SH, van Dijk JMC, Potgieser ARE, Satomi J, Tada Y, Phelps R, Abla A, Winkler E, Du R, Lai PMR, Zipfel GJ, Derdeyn C, Samaniego EA.

Background: Anterior cranial fossa dural arteriovenous fistulas (ACF-dAVFs) are aggressive vascular lesions. The pattern of venous drainage is the most important determinant of symptoms. Due to the absence of a venous sinus in the anterior cranial fossa, most ACF-dAVFs have some degree of drainage through small cortical veins. We describe the natural history, angiographic presentation and outcomes of the largest cohort of ACF-dAVFs.
Methods: The CONDOR consortium includes data from 12 international centers. Patients included in the study were diagnosed with an arteriovenous fistula between 1990-2017. ACF-dAVFs were selected from a cohort of 1077 arteriovenous fistulas. The presentation, angioarchitecture and treatment outcomes of ACF-dAVF were extracted and analyzed.
Results: 60 ACF-dAVFs were included in the analysis. Most ACF-dAVFs were symptomatic (38/60, 63%). The most common symptomatic presentation was intracranial hemorrhage (22/38, 57%). Most ACF-dAVFs drained through cortical veins (85%, 51/60), which in most instances drained into the superior sagittal sinus (63%, 32/51). The presence of cortical venous drainage predicted symptomatic presentation (OR 9.4, CI 1.98 to 69.1, p=0.01). Microsurgery was the most effective modality of treatment. 56% (19/34) of symptomatic patients who were treated had complete resolution of symptoms. Improvement of symptoms was not observed in untreated symptomatic ACF-dAVFs.
Conclusion: Most ACF-dAVFs have a symptomatic presentation. Drainage through cortical veins is a key angiographic feature of ACF-dAVFs that accounts for their malignant course. Microsurgery is the

most effective treatment. Due to the high risk of bleeding, closure of ACF-dAVFs is indicated regardless of presentation.

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Impact factor: 4.9 ; Q1

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33. Dural Arteriovenous Fistulas With Cognitive Impairment: Angiographic Characteristics and Treatment Outcomes
Sanchez S, Wendt L, Hayakawa M, Chen CJ, Sheehan JP, Kim LJ, Abecassis IJ, Levitt MR, Meyer RM, Guniganti R, Kansagra AP, Lanzino G, Giordan E, Brinjikji W, Bulters DO, Durnford A, Fox WC, Smith J, Polifka AJ, Gross B, Amin-Hanjani S, Alaraj A, Kwasnicki A, Starke RM, Chen SH, van Dijk JMC, Potgieser ARE, Satomi J, Tada Y, Phelps R, Abla A, Winkler E, Du R, Rosalind Lai PM, Ortega-Gutierrez S, Zipfel GJ, Derdeyn C, Samaniego EA.

Background and objectives: Anecdotal cases of rapidly progressing dementia in patients with dural arteriovenous fistulas (dAVFs) have been reported in small series. However, large series have not characterized these dAVFs. We conducted an analysis of the largest cohort of dAVFs presenting with cognitive impairment (dAVFs-CI), aiming to provide a detailed characterization of this subset of dAVFs.
Methods: Patients with dAVFs-CI were analyzed from the CONDOR Consortium, a multicenter repository comprising 1077 dAVFs. A propensity score matching analysis was conducted to compare dAVFs-CI with Borden type II and type III dAVFs without cognitive impairment (controls). Logistic regression was used to identify angiographic characteristics specific to dAVFs-CI. Furthermore, post-treatment outcomes were analyzed.
Results: A total of 60 patients with dAVFs-CI and 60 control dAVFs were included. Outflow obstruction leading to venous hypertension was observed in all dAVFs-CI. Sinus stenosis was significantly associated with dAVFs-CI (OR 2.85, 95% CI: 1.16-7.55, P = .027). dAVFs-CI were more likely to have a higher number of arterial feeders (OR 1.56, 95% CI 1.22-2.05, P < .001) and draining veins (OR 2.05, 95% CI 1.05-4.46, P = .004). Venous ectasia increased the risk of dAVFs-CI (OR 2.38, 95% CI 1.13-5.11, P = .024). A trend toward achieving asymptomatic status at follow-up was observed in patients with successful closure of dAVFs (OR 2.86, 95% CI 0.85-9.56, P = .09).
Conclusion: Venous hypertension is a key angiographic feature of dAVFs-CI. Moreover, these fistulas present at a mean age of 58 years-old, and exhibit a complex angioarchitecture characterized by an increased number of arteriovenous connections and stenosed sinuses. The presence of venous ectasia further exacerbates the impaired drainage and contributes to the development of dAVFs-CI. Notably, in certain cases, closure of the dAVF has the potential to reverse symptoms.

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Impact factor: 4.8 ; Q1

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34. Subacute cognitive impairment after first-ever transient ischemic attack or ischemic stroke in young adults: The ODYSSEY study
Schellekens MM, Boot EM, Verhoeven JI, Ekker MS, van Alebeek ME, Brouwers PJ, Arntz RM, van Dijk GW, Gons RA, van Uden IW, den Heijer T, de Kort PL, de Laat KF, van Norden A, Vermeer SE, van Zagten MS, van Oostenbrugge RJ, Wermer MJ, Nederkoorn PJ, van Rooij FG, van den Wijngaard IR, de Leeuw FE, Kessels RP, Tuladhar AM.

Introduction: We aimed to investigate the prevalence of cognitive impairment in the subacute phase after transient ischemic attack (TIA) and ischemic stroke (IS), factors associated with a vascular

cognitive disorder, and the prevalence of subjective cognitive complaints and their relation with objective cognitive performance.
Patients and methods: In this multicenter prospective cohort study, we recruited patients with first-ever TIA and IS, aged 18-49 years, between 2013 and 2021 for cognitive assessment up to 6 months after index event. We calculated composite Z-scores for seven cognitive domains. We defined cognitive impairment as a composite Z-score < -1.5. We defined major vascular cognitive disorder as a Z-score < -2.0 in one or more cognitive domains.
Results: Fifty three TIA and 545 IS patients completed cognitive assessment with mean time to assessment of 89.7 (SD 40.7) days. The median NIHSS at admission was 3 (interquartile range, 1-5). Cognitive impairment was common in five domains (up to 37%), with similar proportion in TIA and IS patients. Patients with major vascular cognitive disorder had a lower education level, higher NIHSS scores and more frequent lesions in the left frontotemporal lobe than without vascular cognitive disorder ($p < 0.05$ FDR-corrected). Subjective memory and executive cognitive complaints were present in about two-thirds of the patients, but were weakly associated with objective cognitive performance (β: -0.32 and -0.21, respectively).
Discussion and conclusion: In the subacute phase after TIA or stroke in young adults, cognitive impairment and subjective cognitive complaints are prevalent, but they are weakly associated with each other.

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Impact factor: 6.1 ; Q1

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35. Cognitive trajectory in the first year after first-ever ischaemic stroke in young adults: the ODYSSEY study
Schellekens MMI, Springer RCS, Boot EM, Verhoeven JI, Ekker MS, van Alebeek ME, Brouwers P, Arntz RM, van Dijk GW, Gons RAR, van Uden IWM, den Heijer T, van Tuijl JH, de Laat KF, van Norden AGW, Vermeer SE, van Zagten MSG, Van Oostenbrugge RJ, Wermer MJH, Nederkoorn PJ, van Rooij FG, van den Wijngaard IR, de Kort PLM, De Leeuw FE, Kessels RPC, Tuladhar AM.

Background: Limited data exists on cognitive recovery in young stroke patients. We aimed to investigate the longitudinal course of cognitive performance during the first year after stroke at young age and identify predictors for cognitive recovery.
Methods: We conducted a multicentre prospective cohort study between 2013 and 2021, enrolling patients aged 18-49 years with first-ever ischaemic stroke. Cognitive assessments were performed within 6 months and after 1 year following the index event, covering seven cognitive domains. Composite Z-scores using normative data determined cognitive impairment (Z-score<-1.5). A Reliable Change Index (RCI) assessed cognitive recovery (RCI>1.96) or decline (RCI<-1.96).
Results: 393 patients (median age 44.3 years, IQR 38.4-47.2) completed cognitive assessments with a median time interval of 403 days (IQR 364-474) between assessments. Based on RCI, a similar proportion of patients showed improvement and decline in each cognitive domain, while the majority exhibited no cognitive change. Among cognitively impaired patients at baseline, improvements were observed in processing speed (23.1%), visuoconstruction (40.1%) and executive functioning (20.0%). Younger age was associated with better cognitive recovery in visuoconstruction, and larger lesion volume was related to cognitive recovery in processing speed. No other predictors for cognitive recovery were identified.
Conclusions: Cognitive impairment remains prevalent in young stroke even 1 year after the event. Most patients showed no cognitive change, however, recovery may have occurred in the early weeks after stroke, which was not assessed in our study. Among initially cognitively impaired patients, cognitive recovery is observed in processing speed, visuoconstruction and executive functioning. It is still not possible to predict cognitive recovery in individual patients.

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Impact factor: 11.1 ; Q1

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36. Cortical excitation/inhibition ratios in patients with major depression treated with electroconvulsive therapy: an EEG analysis
Stuiver S, Pottkämper JCM, Verdijk J, Ten Doesschate F, Aalbregt E, van Putten M, Hofmeijer J, van Waarde JA.

Electroconvulsive therapy (ECT) is an effective treatment for major depression, but its working mechanisms are poorly understood. Modulation of excitation/inhibition (E/I) ratios may be a driving factor. Here, we estimate cortical E/I ratios in depressed patients and study whether these ratios change over the course of ECT in relation to clinical effectiveness. Five-minute resting-state electroencephalography (EEG) recordings of 28 depressed patients were recorded before and after their ECT course. Using a novel method based on critical dynamics, functional E/I (fE/I) ratios in the frequency range of 0.5-30 Hz were estimated in frequency bins of 1 Hz for the whole brain and for pre-defined brain regions. Change in Hamilton Depression Rating Scale (HDRS) score was used to estimate clinical effectiveness. To account for test-retest variability, repeated EEG recordings from an independent sample of 31 healthy controls (HC) were included. At baseline, no differences in whole brain and regional fE/I ratios were found between patients and HC. At group level, whole brain and regional fE/I ratios did not change over the ECT course. However, in responders, frontal fE/I ratios in the frequencies 12-28 Hz increased significantly ($p(FDR) < 0.05$ [FDR = false discovery rate]) over the ECT course. In non-responders and HC, no changes occurred over time. In this sample, frontal fE/I ratios increased over the ECT course in relation to treatment response. Modulation of frontal fE/I ratios may be an important mechanism of action of ECT.

Gepubliceerd: Eur Arch Psychiatry Clin Neurosci. 2023.
Impact factor: 4.7 ; Q1

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37. Early EEG monitoring predicts clinical outcome in patients with moderate to severe traumatic brain injury
Tewarie PKB, Beernink TMJ, Eertman-Meyer CJ, Cornet AD, Beishuizen A, van Putten M, Tjepkema-Cloostermans MC.

There is a need for reliable predictors in patients with moderate to severe traumatic brain injury to assist clinical decision making. We assess the ability of early continuous EEG monitoring at the intensive care unit (ICU) in patients with traumatic brain injury (TBI) to predict long term clinical outcome and evaluate its complementary value to current clinical standards. We performed continuous EEG measurements in patients with moderate to severe TBI during the first week of ICU admission. We assessed the Extended Glasgow Outcome Scale (GOSE) at 12 months, dichotomized into poor (GOSE 1-3) and good (GOSE 4-8) outcome. We extracted EEG spectral features, brain symmetry index, coherence, aperiodic exponent of the power spectrum, long range temporal correlations, and broken detailed balance. A random forest classifier using feature selection was trained to predict poor clinical outcome based on EEG features at 12, 24, 48, 72 and 96 h after trauma. We compared our predictor with the IMPACT score, the best available predictor, based on clinical, radiological and laboratory findings. In addition we created a combined model using EEG as well as the clinical, radiological and laboratory findings. We included hundred-seven patients. The best prediction model using EEG parameters was found at 72 h after trauma with an AUC of 0.82 (0.69-0.92), specificity of 0.83 (0.67-0.99) and sensitivity of 0.74 (0.63-0.93). The IMPACT score predicted poor outcome with an AUC of 0.81 (0.62-0.93), sensitivity of 0.86 (0.74-0.96) and specificity

of 0.70 (0.43-0.83). A model using EEG and clinical, radiological and laboratory parameters resulted in a better prediction of poor outcome ($p < 0.001$) with an AUC of 0.89 (0.72-0.99), sensitivity of 0.83 (0.62-0.93) and specificity of 0.85 (0.75-1.00). EEG features have potential use for predicting clinical outcome and decision making in patients with moderate to severe TBI and provide complementary information to current clinical standards.

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Impact factor: 4.2 ; Q2

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38. Preservation of thalamocortical circuitry is essential for good recovery after cardiac arrest
Tewarie PKB, Tjepkema-Cloostermans MC, Abeysuriya RG, Hofmeijer J, van Putten M.

Continuous electroencephalographam (EEG) monitoring contributes to prediction of neurological outcome in comatose cardiac arrest survivors. While the phenomenology of EEG abnormalities in postanoxic encephalopathy is well known, the pathophysiology, especially the presumed role of selective synaptic failure, is less understood. To further this understanding, we estimate biophysical model parameters from the EEG power spectra from individual patients with a good or poor recovery from a postanoxic encephalopathy. This biophysical model includes intracortical, intrathalamic, and corticothalamic synaptic strengths, as well as synaptic time constants and axonal conduction delays. We used continuous EEG measurements from hundred comatose patients recorded during the first 48 h postcardiac arrest, 50 with a poor neurological outcome [cerebral performance category (CPC = 5)] and 50 with a good neurological outcome (CPC = 1). We only included patients that developed (dis-)continuous EEG activity within 48 h postcardiac arrest. For patients with a good outcome, we observed an initial relative excitation in the corticothalamic loop and corticothalamic propagation that subsequently evolved towards values observed in healthy controls. For patients with a poor outcome, we observed an initial increase in the cortical excitation-inhibition ratio, increased relative inhibition in the corticothalamic loop, delayed corticothalamic propagation of neuronal activity, and severely prolonged synaptic time constants that did not return to physiological values. We conclude that the abnormal EEG evolution in patients with a poor neurological recovery after cardiac arrest may result from persistent and selective synaptic failure that includes corticothalamic circuitry and also delayed corticothalamic propagation.

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Impact factor: onbekend

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39. Collateral status and recanalization after endovascular treatment for acute ischemic stroke
Uniken Venema SM, Dankbaar JW, Wolff L, van Es A, Sprengers M, van der Lugt A, Dippel DWJ, van der Worp HB, MR CLEAN Registry investigators: Brouwers P, Bulut T.

Background: Successful recanalization and good collateral status are associated with good clinical outcomes after endovascular treatment (EVT) for acute ischemic stroke, but the relationships among them are unclear.
Objective: To assess if collateral status is associated with recanalization after EVT and if collateral status modifies the association between successful recanalization and functional outcome.
Methods: We retrospectively analyzed data from the MR CLEAN Registry, a multicenter prospective cohort study of patients with a proximal anterior occlusion who underwent EVT in the Netherlands. We determined collateral status with a previously validated four-point visual grading scale and defined successful recanalization as an extended Thrombolysis in Cerebral Infarction score ≥2B. Functional outcome was determined using the modified Rankin Scale score at 90 days. We assessed,

with multivariable logistic regression models, the associations between (1) collateral status and successful recanalization, (2) successful recanalization and functional outcome, (3) collateral status and functional outcome. An interaction of collateral status and successful recanalization was assessed. Subgroup analyses were performed for patients treated with intravenous thrombolysis.
Results: We included 2717 patients, of whom 1898 (70%) had successful recanalization. There was no relationship between collateral status and successful recanalization (adjusted common OR (95% CI) of grades 1, 2, and 3 vs 0: 1.19 (0.82 to 1.72), 1.20 (0.83 to 1.75), and 1.10 (0.74 to 1.63), respectively). Successful recanalization (acOR (95% CI): 2.15 (1.84 to 2.52)) and better collateral grades (acOR (95% CI) of grades 1, 2, and 3 vs 0: 2.12 (1.47 to 3.05), 3.46 (2.43 to 4.92), and 4.16 (2.89 to 5.99), respectively) were both associated with a shift towards better functional outcome, without an interaction between collateral status and successful recanalization. Results were similar for the subgroup of thrombolysed patients.
Conclusions: Collateral status is not associated with the probability of successful recanalization after EVT and does not modify the association between successful recanalization and functional outcome.

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Impact factor: 4.9 ; Q1

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40. Atrial fibrillation detected with outpatient cardiac rhythm monitoring in patients with ischemic stroke or TIA of undetermined cause
van der Maten G, Meijs MFL, van der Palen J, Brouwers P, von Birgelen C, van Opstal J, den Hertog HM.

Objectives: Guidelines advise cardiac rhythm monitoring for 3 up to 30 days for detecting atrial fibrillation (AF) in patients with ischemic stroke of undetermined cause. However, the optimal monitoring duration is unknown. We aimed to determine the AF detection rate during 7-day outpatient cardiac rhythm monitoring in this patient group.
Methods: Participants from a large tertiary hospital in a prospective observational study (ATTEST) underwent outpatient cardiac rhythm monitoring after a negative standard diagnostic evaluation (i.e., 12-lead electrocardiogram and in-hospital telemetry). Primary outcome was the rate of newly detected AF.
Results: We examined 373 patients [age: 67.8±11.6 years; women: 166(44.5%); stroke: 278(74.5%)]. Median monitoring duration was 7 days (Inter Quartile Range (IQR) 7-7), performed after median of 36 days (IQR 27-47). AF was newly detected in 17(4.6%) patients, 5.4% of patients with ischemic stroke and 2.1% of patients with TIA. 53% of AF was detected on day-1, after day-3 73% of new AF was found. First AF episodes were detected up to day-7. Diabetes and increasing age were independent predictors of new AF.
Conclusion: After ischemic stroke or TIA of undetermined cause, 7-day outpatient cardiac rhythm monitoring detected new AF in 4.6%. Patients with AF had significantly more cardiovascular risk factors. Although about 50% of first AF episodes occurred during the first day of monitoring, new AF was detected up to day-7, implying that the recommended minimum of 3 days cardiac rhythm monitoring after ischemic stroke of undetermined cause is insufficient. Subsequent long-term rhythm monitoring should be considered in selected patients.

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Impact factor: 2.5 ; Q3

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41. Cognition, emotional state, and quality of life of survivors after cardiac arrest with rhythmic and periodic EEG patterns
van Gils PCW, Ruijter BJ, Bloo RJK, van Putten M, Foudraine NA, van Hout MSE, Tromp SC, van Mook W, Rouhl RPW, van Heugten CM, Hofmeijer J.

Aim: Rhythmic and periodic patterns (RPPs) on the electroencephalogram (EEG) in comatose patients after cardiac arrest have been associated with high case fatality rates. A good neurological outcome according to the Cerebral Performance Categories (CPC) has been reported in up to 10% of cases. Data on cognitive, emotional, and quality of life outcomes are lacking. We aimed to provide insight into these outcomes at one-year follow-up.
Methods: We assessed outcome of surviving comatose patients after cardiac arrest with RPPs included in the 'treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation' (TELSTAR) trial at one-year follow-up, including the CPC for functional neurological outcome, a cognitive assessment, the hospital anxiety and depression scale (HADS) for emotional outcomes, and the 36-item short-form health survey (SF-36) for quality of life. Cognitive impairment was defined as a score of more than 1.5 SD below the mean on ≥ 2 (sub)tests within a cognitive domain.
Results: Fourteen patients were included (median age 58 years, 21% female), of whom 13 had a cognitive impairment. Eleven of 14 were impaired in memory, 9/14 in executive functioning, and 7/14 in attention. The median scores on the HADS and SF-36 were all worse than expected. Based on the CPC alone, 8/14 had a good outcome (CPC 1-2).
Conclusion: Nearly all cardiac arrest survivors with RPPs during the comatose state have cognitive impairments at one-year follow-up. The incidence of anxiety and depression symptoms seem relatively high and quality of life relatively poor, despite 'good' outcomes according to the CPC.

Gepubliceerd: Resuscitation. 2023;189:109830.
Impact factor: 6.5 ; Q1

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42. Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone
van Kranendonk KR, Kappelhof M, Bruggeman AAE, Rinkel LA, Treurniet KM, LeCouffe N, Emmer BJ, Coutinho JM, Wolff L, van Zwam WH, van Oostenbrugge RJ, van der Lugt A, Dippel DWJ, Roos Y, Marquering HA, Majoie C, MR CLEAN-NO IV Investigators: Brouwers P, Bulut T.

Background: Intravenous alteplase treatment (IVT) for acute ischemic stroke carries a risk of intracranial hemorrhage (ICH). However, reperfusion of an occluded vessel itself may contribute to the risk of ICH. We determined whether IVT and reperfusion are associated with ICH or its volume in the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN)-NO IV trial.
Methods: The MR CLEAN-NO IV trial randomized patients with acute ischemic stroke due to large vessel occlusion to receive either IVT followed by endovascular treatment (EVT) or EVT alone. ICH was classified according to the Heidelberg bleeding classification on follow-up MRI or CT approximately 8 hours-7 days after stroke. Hemorrhage volume was measured with ITK-snap. Successful reperfusion was defined as extended Thrombolysis In Cerebral Infarction (eTICI) score of 2b-3. Multinomial and binary adjusted logistic regression were used to determine the association of IVT and reperfusion with ICH subtypes.
Results: Of 539 included patients, 173 (32%) developed ICH and 30 suffered from symptomatic ICH (sICH) (6%). Of the patients with ICH, 102 had hemorrhagic infarction, 47 had parenchymal hematoma, 44 had SAH, and six had other ICH. Reperfusion was associated with a decreased risk of SAH, and IVT was not associated with SAH (eTICI 2b-3: adjusted OR 0.45, 95% CI 0.21 to 0.97; EVT without IVT: OR 1.6, 95% CI 0.91 to 2.8). Reperfusion status and IVT were not associated with overall

ICH, hemorrhage volume, and sICH (sICH: EVT without IVT, OR 0.96, 95% CI 0.41 to 2.25; eTICI 2b-3, OR 0.49, 95% CI 0.23 to 1.05).
Conclusion: Neither IVT administration before EVT nor successful reperfusion after EVT were associated with ICH, hemorrhage volume, and sICH. SAH occurred more often in patients for whom successful reperfusion was not achieved.

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Impact factor: 4.9 ; Q1

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43. Prognostic Value of Thrombus Volume and Interaction With First-Line Endovascular Treatment Device Choice
van Voorst H, Bruggeman AAE, Andriessen J, Hoving JW, Konduri PR, Yang W, Kappelhof M, Arrarte Terreros N, Roos Y, van Zwam WH, van der Lugt A, van der Hoorn A, Boiten J, Roosendaal S, Jenniskens S, Caan MWA, Marquering HA, Emmer BJ, Majoie C, MR CLEAN Registry investigators: Brouwers P, Bulut T.

Background: A larger thrombus in patients with acute ischemic stroke might result in more complex endovascular treatment procedures, resulting in poorer patient outcomes. Current evidence on thrombus volume and length related to procedural and functional outcomes remains contradicting. This study aimed to assess the prognostic value of thrombus volume and thrombus length and whether this relationship differs between first-line stent retrievers and aspiration devices for endovascular treatment.
Methods: In this multicenter retrospective cohort study, 670 of 3279 patients from the MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) for endovascularly treated large vessel occlusions were included. Thrombus volume (0.1 mL) and length (0.1 mm) based on manual segmentations and measurements were related to reperfusion grade (expanded Treatment in Cerebral Infarction score) after endovascular treatment, the number of retrieval attempts, symptomatic intracranial hemorrhage, and a shift for functional outcome at 90 days measured with the reverted ordinal modified Rankin Scale (odds ratio >1 implies a favorable outcome). Univariable and multivariable linear and logistic regression were used to report common odds ratios (cORs)/adjusted cOR and regression coefficients (B/aB) with 95% CIs. Furthermore, a multiplicative interaction term was used to analyze the relationship between first-line device choice, stent retrievers versus aspiration device, thrombus volume, and outcomes.
Results: Thrombus volume was associated with functional outcome (adjusted cOR, 0.83 [95% CI, 0.71-0.97]) and number of retrieval attempts (aB, 0.16 [95% CI, 0.16-0.28]) but not with the other outcome measures. Thrombus length was only associated with functional independence (adjusted cOR, 0.45 [95% CI, 0.24-0.85]). Patients with more voluminous thrombi had worse functional outcomes if endovascular treatment was based on first-line stent retrievers (interaction cOR, 0.67 [95% CI, 0.50-0.89]; *P*=0.005; adjusted cOR, 0.74 [95% CI, 0.55-1.0]; *P*=0.04).
Conclusions: In this study, patients with a more voluminous thrombus required more endovascular thrombus retrieval attempts and had a worse functional outcome. Patients with a lengthier thrombus were less likely to achieve functional independence at 90 days. For more voluminous thrombi, first-line stent retrieval compared with first-line aspiration might be associated with worse functional outcome.

Gepubliceerd: Stroke. 2023;54(4):1056-65.
Impact factor: 8.4 ; Q1

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44. Costs and health effects of CT perfusion-based selection for endovascular thrombectomy within 6 hours of stroke onset: a model-based health economic evaluation
van Voorst H, Hoving JW, Koopman MS, Daems JD, Peerlings D, Buskens E, Lingsma H, Marquering HA, de Jong H, Berkhemer OA, van Zwam WH, van Walderveen MAA, van den Wijngaard IR, Dippel DWJ, Yoo AJ, Campbell B, Kunz WG, Majoie CB, Emmer BJ, MR CLEAN Registry investigators: Brouwers P, Bulut T.

Background: Although CT perfusion (CTP) is often incorporated in acute stroke workflows, it remains largely unclear what the associated costs and health implications are in the long run of CTP-based patient selection for endovascular treatment (EVT) in patients presenting within 6 hours after symptom onset with a large vessel occlusion.
Methods: Patients with a large vessel occlusion were included from a Dutch nationwide cohort (n=703) if CTP imaging was performed before EVT within 6 hours after stroke onset. Simulated cost and health effects during 5 and 10 years follow-up were compared between CTP based patient selection for EVT and providing EVT to all patients. Outcome measures were the net monetary benefit at a willingness-to-pay of €80 000 per quality-adjusted life year, incremental cost-effectiveness ratio), difference in costs from a healthcare payer perspective (ΔCosts) and quality-adjusted life years (ΔQALY) per 1000 patients for 1000 model iterations as outcomes.
Results: Compared with treating all patients, CTP-based selection for EVT at the optimised ischaemic core volume (ICV≥110 mL) or core-penumbra mismatch ratio (MMR≤1.4) thresholds resulted in losses of health (median ΔQALYs for ICV≥110 mL: -3.3 (IQR: -5.9 to -1.1), for MMR≤1.4: 0.0 (IQR: -1.3 to 0.0)) with median ΔCosts for ICV≥110 mL of -€348 966 (IQR: -€712 406 to -€51 158) and for MMR≤1.4 of €266 513 (IQR: €229 403 to €380 110)) per 1000 patients. Sensitivity analyses did not yield any scenarios for CTP-based selection of patients for EVT that were cost-effective for improving health, including patients aged ≥80 years CONCLUSION: In EVT-eligible patients presenting within 6 hours after symptom onset, excluding patients based on CTP parameters was not cost-effective and could potentially harm patients.

Gepubliceerd: J Neurol Neurosurg Psychiatry. 2023.
Impact factor: 11.1 ; Q1

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45. Choice of Implantable Pulse Generators for Deep Brain Stimulation: An Overview of Clinical Practice
Willems YR, van der Gaag NA, Kho KH, Tveiten Ø V, Krüger MT, Jakobs M.

Introduction: The success of deep brain stimulation (DBS) treatment depends on several factors, including proper patient selection, accurate electrode placement, and adequate stimulation settings. Another factor that may impact long-term satisfaction and therapy outcomes is the type of implantable pulse generator (IPG) used: rechargeable or non-rechargeable. However, there are currently no guidelines on the choice of IPG type. The present study investigates the current practices, opinions, and factors DBS clinicians consider when choosing an IPG for their patients.
Methods: Between December 2021 and June 2022, we sent a structured questionnaire with 42 questions to DBS experts of two international, functional neurosurgery societies. The questionnaire included a rating scale where participants could rate the factors influencing their choice of IPG type and their satisfaction with certain IPG aspects. Additionally, we presented four clinical case scenarios to assess preference of choice of IPG-type in each case.
Results: Eighty-seven participants from 30 different countries completed the questionnaire. The three most relevant factors for IPG choice were "existing social support," "cognitive status," and "patient age." Most participants believed that patients valued avoiding repetitive replacement surgeries more than the burden of regularly recharging the IPG. Participants reported that they implanted the same amount of rechargeable as non-rechargeable IPGs for primary DBS insertions and 20% converted

non-rechargeable to rechargeable IPGs during IPG replacements. Most participants estimated that rechargeable was the more cost-effective option.
Conclusion: This present study shows that the decision-making of the choice of IPG is very individualized. We identified the key factors influencing the physician's choice of IPG. Compared to patient-centric studies, clinicians may value different aspects. Therefore, clinicians should rely not only on their opinion but also counsel patients on different types of IPGs and consider the patient's preferences. Uniform global guidelines on IPG choice may not represent regional or national differences in the healthcare systems.

Gepubliceerd: Stereotact Funct Neurosurg. 2023;101(2):135-45.
Impact factor: 1.7 ; Q3

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46. QUality of life and Economic evaluation after neuroSTimulation for Epilepsy (QUESTE) in adolescents and adults with drug-resistant epilepsy: protocol for a multicentre, prospective observational cohort study in The Netherlands
Smeets JJAS, Rijkers K, Ackermans L, Schijns O, van Mastrigt GAPG, Rouhl R, Wagner GL, van Kuijk S, Nelissen J, van Straaten IECW, Kho K, Snoeijen-Schouwenaars F, Meppelink AM, Klinkenberg S, Majoie HJM.

Introduction: Epilepsy is one of the most common chronic neurological disorders. Antiseizure medication (ASM) is the first choice of treatment, however, 30% of epilepsy patients are drug-resistant. For these patients, neuromodulation can be an option, especially when epilepsy surgery is not possible or did not lead to seizure freedom. Epilepsy is associated with reduced quality of life (QoL), which heavily depends on seizure control.The most recent Cochrane reviews have shown that vagus nerve stimulation and deep brain stimulation of the anterior nucleus of the thalamus, lead to a responder rate OR of, respectively, 1.93 and 1.20. The question arises if neuromodulation for drug-resistant epilepsy (DRE) will be more cost-effective than sole treatment with ASM. The current study aims to determine the change in QoL after neuromodulation. Secondarily, we will aim to study the cost-effectiveness of these treatments.
Methods and analysis: This prospective cohort study aims at including 100 patients aged 16 or above who will be referred for neuromodulation, from January 2021 to January 2026. After informed consent, QoL and other relevant parameters will be assessed at baseline, 6 months, 1, 2 and 5 years after surgery. Data on seizure frequency will be derived from patient charts. We expect that DRE patients will report better QoL after neuromodulation. Even if they would still report seizures, the treatment can be seen as useful. This is especially true when patients can participate in society again to a greater extent than before treatment.
Ethics and dissemination: The board of directors of participating centres all gave permission for this study to commence. The medical ethics committees decided that this study does not fall under the Medical Research Involving Human Subjects Act (WMO). The findings of this study will be presented at (inter)national conferences and in peer-reviewed journals.
Trial registration number: NL9033.

Gepubliceerd: BMJ Open 2023;13(6):e071575.
Impact factor: 2.4 ; Q1

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47. Safety and technical efficacy of early minimally invasive endoscopy-guided surgery for intracerebral haemorrhage: the Dutch Intracerebral haemorrhage Surgery Trial pilot study

Sondag L, Schreuder FHBM, Pegge SAH, Coutinho JM, Dippel DWJ, Janssen PM, Vandertop WP, Boogaard HD, Dammers R, Klijn CJM, Dutch ICH Surgery Trial Study group, part of the CONTRAST consortium: Kho KH.

Background: Previous randomised controlled trials could not demonstrate that surgical evacuation of intracerebral haemorrhage (ICH) improves functional outcome. Increasing evidence suggests that minimally invasive surgery may be beneficial, in particular when performed early after symptom onset. The aim of this study was to investigate safety and technical efficacy of early minimally invasive endoscopy-guided surgery in patients with spontaneous supratentorial ICH.
Methods: The Dutch Intracerebral Haemorrhage Surgery Trial pilot study was a prospective intervention study with blinded outcome assessment in three neurosurgical centres in the Netherlands. We included adult patients with spontaneous supratentorial ICH ≥10mL and National Institute of Health Stroke Scale (NIHSS) score ≥2 for minimally invasive endoscopy-guided surgery within 8 h after symptom onset in addition to medical management. Primary safety outcome was death or increase in NIHSS ≥4 points at 24 h. Secondary safety outcomes were procedure-related serious adverse events (SAEs) within 7 days and death within 30 days. Primary technical efficacy outcome was ICH volume reduction (%) at 24 h.
Results: We included 40 patients (median age 61 years; IQR 51-67; 28 men). Median baseline NIHSS was 19.5 (IQR 13.3-22.0) and median ICH volume 47.7mL (IQR 29.4-72.0). Six patients had a primary safety outcome, of whom two already deteriorated before surgery and one died within 24 h. Sixteen other SAEs were reported within 7 days in 11 patients (of whom two patients that already had a primary safety outcome), none device related. In total, four (10%) patients died within 30 days. Median ICH volume reduction at 24 h was 78% (IQR 50-89) and median postoperative ICH volume 10.5mL (IQR 5.1-23.8).
Conclusions: Minimally invasive endoscopy-guided surgery within 8 h after symptom onset for supratentorial ICH appears to be safe and can effectively reduce ICH volume. Randomised controlled trials are needed to determine whether this intervention also improves functional outcome.
Trial registration: Clinicaltrials.gov : NCT03608423, August 1st, 2018.

Gepubliceerd: Acta Neurochir (Wien) 2023;165(6):1585-1596.
Impact factor: 1.9 ; Q3

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48. Functional brain connectivity in young adults with post-stroke epilepsy
Boot EM, Omes QPM, Maaijwee N, Schaapsmeerders P, Arntz RM, Rutten-Jacobs LCA, Kessels RPC, de Leeuw FE, Tuladhar AM.

Approximately 1 in 10 young stroke patients (18-50 years) will develop post-stroke epilepsy, which is associated with cognitive impairment. While previous studies have shown altered brain connectivity in patients with epilepsy, little is however known about the changes in functional brain connectivity in young stroke patients with post-stroke epilepsy and their relationship with cognitive impairment. Therefore, we aimed to investigate whether young ischaemic stroke patients have altered functional networks and whether this alteration is related to cognitive impairment. We included 164 participants with a first-ever cerebral infarction at young age (18-50 years), along with 77 age- and sex-matched controls, from the Follow-Up of Transient Ischemic Attack and Stroke patients and Unelucidated Risk Factor Evaluation study. All participants underwent neuropsychological testing and resting-state functional MRI to generate functional connectivity networks. At follow-up (10.5 years after the index event), 23 participants developed post-stroke epilepsy. Graph theoretical analysis revealed functional network reorganization in participants with post-stroke epilepsy, in whom a weaker (i.e. network strength), less-integrated (i.e. global efficiency) and less-segregated (i.e. clustering coefficient and local efficiency) functional network was observed compared with the participants without post-stroke epilepsy group and the controls ($P < 0.05$). Regional analysis showed

a trend towards decreased clustering coefficient, local efficiency and nodal efficiency in contralesional brain regions, including the caudal anterior cingulate cortex, posterior cingulate cortex, precuneus, superior frontal gyrus and insula in participants with post-stroke epilepsy compared with those without post-stroke epilepsy. Furthermore, participants with post-stroke epilepsy more often had impairment in the processing speed domain than the group without post-stroke epilepsy, in whom the network properties of the precuneus were positively associated with processing speed performance. Our findings suggest that post-stroke epilepsy is associated with functional reorganization of the brain network after stroke that is characterized by a weaker, less-integrated and less-segregated brain network in young ischaemic stroke patients compared with patients without post-stroke epilepsy. The contralesional brain regions, which are mostly considered as hub regions, might be particularly involved in the altered functional network and may contribute to cognitive impairment in post-stroke epilepsy patients. Overall, our findings provide additional evidence for a potential role of disrupted functional network as underlying pathophysiological mechanism for cognitive impairment in patients with post-stroke epilepsy.

Gepubliceerd: Brain Commun 2023;5(6):fcad277.
Impact factor: 4.1 ; Q1

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49. Dynamic phase-locking states and personality in sub-acute mild traumatic brain injury: An exploratory study
van der Horn HJ, de Koning ME, Visser K, Kok MGJ, Spikman JM, Scheenen ME, Renken RJ, Calhoun VD, Vergara VM, Cabral J, Mayer AR, van der Naalt J.

Research has shown that maladaptive personality characteristics, such as Neuroticism, are associated with poor outcome after mild traumatic brain injury (mTBI). The current exploratory study investigated the neural underpinnings of this process using dynamic functional network connectivity (dFNC) analyses of resting-state (rs) fMRI, and diffusion MRI (dMRI). Twenty-seven mTBI patients and 21 healthy controls (HC) were included. After measuring the Big Five personality dimensions, principal component analysis (PCA) was used to obtain a superordinate factor representing emotional instability, consisting of high Neuroticism, moderate Openness, and low Extraversion, Agreeableness, and Conscientiousness. Persistent symptoms were measured using the head injury symptom checklist at six months post-injury; symptom severity (i.e., sum of all items) was used for further analyses. For patients, brain MRI was performed in the sub-acute phase (~1 month) post-injury. Following parcellation of rs-fMRI using independent component analysis, leading eigenvector dynamic analysis (LEiDA) was performed to compute dynamic phase-locking brain states. Main patterns of brain diffusion were computed using tract-based spatial statistics followed by PCA. No differences in phase-locking state measures were found between patients and HC. Regarding dMRI, a trend significant decrease in fractional anisotropy was found in patients relative to HC, particularly in the fornix, genu of the corpus callosum, anterior and posterior corona radiata. Visiting one specific phase-locking state was associated with lower symptom severity after mTBI. This state was characterized by two clearly delineated communities (each community consisting of areas with synchronized phases): one representing an executive/saliency system, with a strong contribution of the insulae and basal ganglia; the other representing the canonical default mode network. In patients who scored high on emotional instability, this relationship was even more pronounced. Dynamic phase-locking states were not related to findings on dMRI. Altogether, our results provide preliminary evidence for the coupling between personality and dFNC in the development of long-term symptoms after mTBI.

Gepubliceerd: PLoS One 2023;18(12):e0295984.
Impact factor: 3.7 ; Q2

Totale impact factor: 629.4
Gemiddelde impact factor: 12.8

Aantal artikelen 1e, 2e of laatste auteur: 12
Totale impact factor: 48.7
Gemiddelde impact factor: 4.1

Orthopedie

1. Ninety-day complication rate based on 532 Latarjet procedures in Dutch hospitals with different operation volumes
Alkaduhimi H, Willigenburg NW, Wessel RN, Wolterbeek N, Veen EJD, Koorevaar RCT, Willems WJ, Nelissen EM, Sonneveld H, Flikweert PE, Pasma JH, Visser CPJ, Meier ME, van den Borne MPJ, Dijkstra AJ, Kraal T, van Noort A, Alta TDW, Gałek-Aldridge MS, Floor S, van den Bekerom MPJ, Eygendaal D.

Background: In this study, we aimed to provide insight into the 90-day complication rates following the Latarjet procedure. Data from 2015 were collected from multiple hospitals in the Netherlands, with different volumes of Latarjet procedures. Our second aim was to examine which patient and surgical factors were associated with complications.
Methods: We conducted a retrospective chart review of 13 hospitals between 2015 and 2022. Data regarding complications within 90 days of Latarjet procedures were extracted. The effect of sex, age, body mass index (BMI), smoking, previous shoulder operations, fixation material, hospital volume, screw size, and operation time on the complication rate was assessed by multivariable logistic regression analysis.
Results: Of the 532 included patients, 58 (10.9%) had complications. The most common complications were material failure (n = 19, 3.6%) and nerve injury (n = 13, 2.4%). The risk of complications was lower for male patients than for female patients (odds ratio, 0.40; 95% confidence interval, 0.21-0.77; P = .006). Age, BMI, smoking, previous shoulder operations, type of fixation material, hospital volume, screw size, and operation time were not associated with complications.
Conclusion: The 90-day complication rate after the Latarjet procedure was 10.9% and was higher in female patients than in male patients. Age, BMI, smoking, previous shoulder operations, type of fixation material, hospital volume, screw size, and operation time did not affect complication rates. We advise setting up a national registry to prevent under-reporting of complications.

Gepubliceerd: J Shoulder Elbow Surg. 2023;32(6):1207-13.
Impact factor: 3.0 ; Q2

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2. Factors Associated With Nonunion in Arthrodesis of the First Metatarsophalangeal Joint: A Multicenter Retrospective Cohort Study
Füssenich W, Seeber GH, van Raaij TM, van Lingen CP, Zuurmond RG, Stevens M, Somford MP.

Background: Arthrodesis of the first metatarsophalangeal joint is the current treatment of choice for symptomatic advanced hallux rigidus and moderate-to-severe hallux valgus. There are different methods to perform arthrodesis, yet no consensus on the best approach. Therefore, this study aimed to determine the effects of preoperative and postoperative hallux valgus angle (HVA), joint preparation and fixation technique, and postoperative immobilization on the incidence of nonunion.
Methods: A retrospective multicenter cohort study was performed that included 794 patients. Univariate and multiple logistic regression was conducted to determine associations between joint preparation, fixation techniques, postoperative immobilization, weightbearing, and pre- and postoperative HVA with nonunion.
Results: Nonunion incidence was 15.2%, with 11.1% symptomatic and revised. Joint preparation using hand instruments (OR 3.75, CI 1.90-7.42) and convex/concave reamers (OR 2.80, CI 1.52-5.16) were associated with greater odds of a nonunion compared to planar cuts. Joint fixation with crossed screws was associated with greater odds of nonunion (OR 2.00, CI 1.11-3.42), as was greater preoperative HVA (OR 1.02, CI 1.00-1.03). However, the latter effect disappeared after inclusion of postoperative HVA in the model, with a small association identified between residual postoperative

HVA and nonunion (OR 1.04, CI 1.01-1.08). Similarly, we found an association between odds of nonunion and higher body weight (OR 1.02, CI 1.01-1.04) but not of body mass index.
Conclusion: Based on our results, first metatarsophalangeal joint arthrodesis with planar cuts and fixation with a plate and interfragmentary screw is associated with the lowest odds of resulting in a nonunion. Higher body weight and greater preoperative HVA were associated with slight increase in rates of nonunion. It is crucial to properly correct the hallux valgus deformity during surgery.

Gepubliceerd: Foot Ankle Int. 2023;44(6):508-15.
Impact factor: 2.7 ; Q2

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3. Letter to the Editor: "Biomechanical Stability of the Sacroiliac Joint With Differing Impact Configurations in a Synthetic Model"
Kampkuiper NFB, Schröder FF, Hekman EEG, Koenrades MA, Nellensteijn JM.

Gepubliceerd: Int J Spine Surg. 2023;17(1):162-3.
Impact factor: 3.5 ; Q onbekend

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4. Active monitoring versus an abduction device for treatment of infants with centered dysplastic hips: study protocol for a randomized controlled trial (TReatment with Active Monitoring (TRAM)-Trial)
Mulder F, Witlox MA, Dirksen CD, de Witte PB, de Vos-Jakobs S, Ham AMT, Witbreuk M, Sakkers R, Drongelen M, Robben SGF, Mathijssen NMC, TRAM-Trial Consortium: den Hartog YM, Zeegers AVCM.

Background: Developmental Dysplasia of the Hip (DDH) is one of the most common pediatric orthopedic disorders, affecting 1-3% of all newborns. The optimal treatment of centered DDH is currently under debate. This randomized controlled trial aims to study the (cost-)effectiveness of active monitoring versus abduction treatment for infants with centered DDH.
Methods: This is a multicenter, parallel-group, open-label, non-inferiority randomized controlled trial studying the (cost-)effectiveness of active monitoring versus abduction treatment for infants with centered DDH in fourteen hospitals in the Netherlands. In total, 800 infants with centered DDH (Graf IIa-/IIb/IIc), aged 10-16 weeks, will be randomly allocated to the active monitoring or abduction treatment group. Infants will be followed up until the age of 24 months. The primary outcome is the rate of normal hips, defined as an acetabular index lower than 25 degrees on an antero-posterior radiograph, at the age of 12 months. Secondary outcomes are the rate of normal hips at the age of 24 months, complications, time to hip normalization, the relation between baseline patient characteristics and the rate of normal hips, compliance, costs, cost-effectiveness, budget impact, health-related quality of life (HRQoL) of the infant, HRQoL of the parents/caregivers, and parent/caregiver satisfaction with the treatment protocol.
Discussion: The outcomes of this randomized controlled trial will contribute to improving current care-as-usual for infants with centered DDH.
Trial registration: Dutch Trial Register, NL9714, registered September 6, 2021. https://clinicaltrialregister.nl/en/trial/29596.

Gepubliceerd: BMC Pediatr. 2023;23(1):203.
Impact factor: 2.4 ; Q2

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5. Inertial-Sensor-Based Monitoring of Sample Entropy and Peak Frequency Changes in Treadmill Walking during Recovery after Total Knee Arthroplasty

van de Ven WAF, Bosga J, Hullegie W, Verra WC, Meulenbroek RGJ.

This study aimed to investigate whether sample entropy (SEn) and peak frequency values observed in treadmill walking could provide physical therapists valuable insights into gait rehabilitation following total knee arthroplasty (TKA). It was recognized that identifying movement strategies that during rehabilitation are initially adaptive but later start to hamper full recovery is critical to meet the clinical goals and minimize the risk of contralateral TKA. Eleven TKA patients were asked to perform clinical walking tests and a treadmill walking task at four different points in time (pre-TKA, 3, 6, and 12 months post-TKA). Eleven healthy peers served as the reference group. The movements of the legs were digitized with inertial sensors and SEn and peak frequency of the recorded rotational velocity-time functions were analyzed in the sagittal plane. SEn displayed a systematic increase during recovery in TKA patients ($p < 0.001$). Furthermore, lower peak frequency ($p = 0.01$) and sample entropy ($p = 0.028$) were found during recovery for the TKA leg. Movement strategies that initially are adaptive, and later hamper recovery, tend to diminish after 12 months post-TKA. It is concluded that inertial-sensor-based SEn and peak frequency analyses of treadmill walking enrich the assessment of movement rehabilitation after TKA.

Gepubliceerd: Sensors (Basel). 2023;23(10).
Impact factor: 3.9 ; Q2

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6. More Predictable and Less Automatized Movements during Walking -not during Repetitive Punching- in Knee Osteoarthritis
van de Ven WAF, Bosga J, Hullegie W, Verra WC, Meulenbroek RGJ.

Using the non-affected leg as stable frame of reference for the affected leg in gait assessment in knee osteoarthritis (KO) fails due to compensatory mechanisms. Assessing the cyclical movements of the upper extremities in a frequency-controlled repetitive punching task may provide an alternative frame of reference in gait assessment in patients with KO. Eleven participants with unilateral KO and eleven healthy controls were asked to perform treadmill walking and repetitive punching. The KO group showed more predictable ($p = 0.020$) and less automatized ($p = 0.007$) movement behavior than controls during treadmill walking. During repetitive punching, the KO group showed a similar degree of predictability ($p = 0.784$) but relative more automatized movement behavior ($p = 0.013$). Thus, the predictability of the movement behavior of the upper extremities during repetitive punching seems unaffected by KO and could provide an alternative frame of reference in gait assessment in patients with KO.

Gepubliceerd: J Mot Behav. 2023;55(5):499-512.
Impact factor: 1.4 ; Q4

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7. The Modified Tampa-Scale of Kinesiophobia for Anterior Shoulder Instability
van Iersel TP, Larsen van Gastel M, Versantvoort A, Hekman KMC, Sierevelt IN, Broekman BFP, van den Bekerom MPJ, Dutch Shoulder Instability Group (DSIG): Govaert, LHM, .

Purpose: To assess content validity and to modify the Tampa Scale of Kinesiophobia (TSK) to make it suitable for application in patients with anterior shoulder instability.
Methods: A four-round Delphi method was performed to establish expert consensus on developing the Tampa Scale of Kinesiophobia for patients with anterior shoulder instability (TSK-SI) using an expert group of Dutch shoulder-specialized orthopedic surgeons and physiotherapists. During round 1, experts were asked to score the 17 items of the original TSK on relevance and construction using

the COSMIN guidelines. With this feedback, questions were reviewed and modified. During round 2, experts were asked to score the modified items. This process was repeated until consensus was established. Then, patients were asked to participate in a moderator-guided, three-step-test interview using a Web-based platform to assess the modified scale. Sessions were recorded and evaluated by the working group. The modified scale was finally adjusted on the basis of the input of these patients.
Results: Thirty Dutch shoulder experts were included, of which 25 completed all 4 rounds, after which consensus was established. One question was added to the modified scale based on feedback in round 1, establishing the 18-item TSK-SI. Sixteen patients with shoulder instability were included, which all completed the three-step test interview. Following this, question 4 (changed to present tense) and question 7 (hypothetical component added) were adjusted, resulting in the final TSK-SI.
Conclusions: This consensus modification of the TSK to TSK-SI can support the content validity of the instrument to assess kinesiophobia in patients with anterior shoulder instability. These modifications may improve the responsiveness and validity of the TSK-SI, as it does not match all the items of the original TSK.
Level of evidence: Level V, consensus statement.

Gepubliceerd: Arthrosc Sports Med Rehabil. 2023;5(4):100768.
Impact factor: onbekend

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8. Anterior deltoid muscle reflection using a deltopectoral approach is safe and does not influence outcome of reverse shoulder arthroplasty
Veen EJD, Smits EJ, Ker A, Whitehouse SL, Ziegenfuss BL, Pivonka P, Gupta A, Cutbush K.

ackground: The deltopectoral approach is well accepted for shoulder arthroplasty procedures. The extended deltopectoral approach with detachment of the anterior deltoid from the clavicle allows increased joint exposure and can protect the anterior deltoid from traction injury. The efficacy of this extended approach has been demonstrated in anatomic total shoulder replacement surgery. However, this has not been shown in reverse shoulder arthroplasty (RSA). The primary aim of this study was to evaluate the safety of the extended deltopectoral approach in RSA. The secondary aim was to evaluate the performance of the deltoid reflection approach in terms of complications and surgical, functional, and radiologic outcomes up to 24 months after surgery.
Methods: A prospective, nonrandomized comparative study was performed between January 2012 and October 2020 including 77 patients in the deltoid reflection group and 73 patients in the comparative group. The decision for inclusion was based on patient and surgeon factors. Complications were recorded. Patients were followed up for ≥24 months to evaluate their shoulder function and undergo ultrasound evaluation. Functional outcome measures included the Oxford Shoulder Score, Disabilities of the Arm, Shoulder and Hand score, American Shoulder and Elbow Surgeons score, pain intensity (rated on visual analog scale [VAS] from 0 to 100), and range of motion (forward flexion, abduction, and external rotation). A regression analysis was performed to evaluate any factors of influence on the VAS score.
Results: There were no significant differences in the complication rate between the 2 groups (14.5% in deltoid reflection group and 13.8% in comparative group, P = .915). Ultrasound evaluation was available in 64 patients (83.1%), and no proximal detachment was observed. In addition, there were no significant differences in functional outcome measures both preoperatively and at 24 months after surgery between the groups assessed based on the mean VAS pain score, Oxford Shoulder Score, Disabilities of the Arm, Shoulder and Hand score, American Shoulder and Elbow Surgeons score, forward flexion, abduction, and external rotation. Adjustment for possible confounders in a regression model indicated that only prior surgery significantly influenced the VAS pain score after surgery (P = .031; 95% confidence interval, 0.574-11.67). Deltoid reflection (P = .068), age (P = .466),

sex (P = .936), use of glenoid graft (P = .091), prosthesis manufacturer (P = .382), and preoperative VAS score (P = .362) were not of influence.
Discussion: The results of this study show that an extended deltopectoral approach for RSA is safe. Selected reflection of the anterior deltoid muscle improved exposure and prevented anterior deltoid muscle injury followed by reattachment. Patients had similar functional scores preoperatively and at 24 months postoperatively compared with a comparative group. Furthermore, ultrasound evaluation showed intact reattachments.

Gepubliceerd: J Shoulder Elbow Surg. 2023;32(6):1135-45.
Impact factor: 3.0 ; Q2

Totale impact factor: 19.9
Gemiddelde impact factor: 2.5

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 1
Totale impact factor: 3.5
Gemiddelde impact factor: 3.5

Plastische chirurgie

1. Revision Incidence after Immediate Direct-to-Implant versus Two-Stage Implant-Based Breast Reconstruction Using National Real-World Data
Becherer BE, Heeg E, Young-Afat DA, Vrancken Peeters M, Rakhorst HA, Mureau MAM.

Background: In immediate implant-based breast reconstruction (IBBR), large variation is observed in current practices between a direct-to-implant and a two-stage approach (insertion of a breast implant after a tissue expander). This population-based study aimed to compare unplanned short- and long-term revision incidence between direct-to-implant and two-stage IBBR in The Netherlands.
Methods: All patients who underwent immediate IBBR following a mastectomy between 2015 and 2019 were selected from the nationwide Dutch Breast Implant Registry. Short- and long-term unplanned revision incidences were studied per immediate IBBR, including revision indications and the total number of additional operations. Confounding by indication was limited using propensity score matching.
Results: A total of 4512 breast implants (3948 women) were included, of which 2100 (47%) were for direct-to-implant IBBR and 2412 (53%) were for two-stage IBBR. Median (IQR) follow-up was 29 months (range, 16 to 45 months) and 33 months (range, 21 to 47 months), respectively. Short-term revision incidence was 4.0% and 11.7%, respectively (conditional OR, 0.31; 95% CI, 0.23 to 0.42%). Long-term revision incidence was 10.6% (95% CI, 9.2 to 12.1%) and 16.4% (95% CI, 14.8 to 17.9%), respectively. In the propensity score-matched cohort, similar results were found. In the direct-to-implant group, more breasts were reconstructed within the planned number of operations than in the two-stage group.
Conclusions: Unplanned revision surgery occurred less often after direct-to-implant IBBR, and more breasts were reconstructed within the planned number of operations compared to two-stage IBBR. These results, based on real-world data, are important for improving patient counseling and shared decision-making.
Clinical question/level of evidence: Risk, II.

Gepubliceerd: Plast Reconstr Surg. 2023;151(4):693-702.
Impact factor: 3.6 ; Q1

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2. Comparing 200,000 Breast Implants and 85,000 Patients over Four National Breast Implant Registries
Becherer BE, Hopper I, Cooter RD, Couturaud B, von Fritschen U, Mullen E, Perks AGB, Pusic AL, Stark B, Mureau MAM, Rakhorst HA.

Background: Growing awareness about breast implant-related adverse events has stimulated the demand for large, independent data resources. For this, data from breast implant registries could be combined. However, that has never been achieved yet.
Methods: Real-world data from four currently active national breast implant registries were used. All permanent breast implants from the Australian, Dutch, Swedish, and American registries were included. A subpopulation present across all registries between 2015 and 2018 was subsequently selected, including only permanent breast implants inserted during primary surgery for breast reconstruction or augmentation in patients without previous breast device surgery. Nationwide coverage, patient and implant characteristics, infection control measures, and revision incidences were analyzed.
Results: A total of 207,189 breast implants were registered. Nationwide coverage varied between 3% and 98%. The subpopulation included 111,590 implants (7% reconstruction, 93% augmentation). Across the registries, mean patient age varied between 41 and 49 years ($P < 0.001$) for

reconstruction and 31 and 36 years (P < 0.001) for augmentation. Variation was observed in implant preferences across the countries and over the years. Infection control measures were most frequently registered in Australia. Cumulative revision incidence at 2 years ranged from 6% to 16% after reconstruction and from 1% to 4% after augmentation.
Conclusions: For the first time, independent, national, registry-based data from four breast implant registries were combined. This is a powerful step forward in optimizing international breast implant monitoring, evidence-based decision-making, and patient safety.

Gepubliceerd: Plast Reconstr Surg. 2023;152(2):307-18.
Impact factor: 3.6 ; Q1

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3. Patients' and Healthcare Professionals' Perspectives on Better Use of Patient-Reported Outcome Measures in Head and Neck Cancer
de Jel DVC, Young-Afat DA, Ooms-Renckens MM, Smeele LE, Rakhorst HA, DHNA study group: van Bemmel AJM.

Objectives: Patients with head and neck cancer (HNC) are often highly affected by disease and treatment, resulting in impaired physical functioning and quality of life. Therefore, evaluation of patients' psychosocial and functional outcomes can be facilitated by patient-reported outcome measures (PROMs). By providing the patients' own perspectives, PROMs are crucial to improving patient-centered care. This study aimed to improve understanding of the perceived value of PROMs in HNC care and how to optimize their clinical value based on patients' and multidisciplinary healthcare professionals' (HCPs) perspectives.
Methods: Population-based surveys among patients with HNC through their patient association and among HCPs nationwide through the Dutch Head and Neck Audit.
Results: A total of 54 patients and 40 multidisciplinary HCPs from all 14 nationwide HNC centers (100%) responded. For patients, the most important element of patient-reported outcome collection systems was including a call to action for those with worse-than-average scores (28%), whereas clinicians found discussing scores during clinical visits the most important (39%). Although 16% of clinicians found short completion time the most important element, none of the patients selected completion time as most important. Additionally, 17% of patients stated completion time was not an issue, provided clinicians would use the outcomes for clinical purposes.
Conclusions: Although patients and clinicians acknowledged the value of patient-reported outcomes, patients would like to be more involved in the clinical implications of their outcomes. Enhancing patients' involvement by a call to action and providing feedback on their scores during outpatient clinic visits may improve the clinical value of PROMs.

Gepubliceerd: Value Health. 2023;26(8):1210-6.
Impact factor: 4.5 ; Q1

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4. Three-phase video-assisted multidisciplinary team debriefing (VAMTD) in high-fidelity blast simulation through the "advocacy and inquiry" method
Gasteratos K, Daniels B, Gebhart SJ, Patterson N, Tarrant MJ, Goverman J, Rakhorst H, der Hulst R.

Introduction: Video-assisted debriefing (VAD) combined with the "advocacy and inquiry" (A&I) technique, is a tool that allows video playback of selected segments of a simulation, thereby assisting the debriefers to structure the session. Currently, however, no consensus exists on how to optimally perform a team debriefing. In our study, we aim to demonstrate and describe the methodology of

A&I debriefing in an instructional simulated blast scenario and assess the impact of VAD on residents' technical and non-technical skills (NTS).
Materials and methods: After Institutional Review Board (IRB) approval, we performed a study with 50 residents who were randomly assigned to two groups. Group 1 (control, or "no VAD", n=25) consisted of residents who received oral debriefing by one independent faculty member without the recorded video of the simulation. Group 2 (intervention, or "VAD", n=25) consisted of residents who received VAD from the second independent faculty member. These residents repeated the same simulation scenario one week after their debrief. Every resident was assessed on the primary and secondary survey, as well as the NTS, based on the integrated skills (IS) score.
Results: The "VAD" group presented significantly higher values for the IS score ($p<0.001$) compared to the "no VAD'' group.
Conclusions: Our demonstration of three-phase VAD emphasizes important aspects of coherent simulation-based training: psychological safety, A&I, reflection, cognitive frames, pre-brief, main debrief, summary, and translation of new discoveries to real-life patient care. The unique audio-visual aspect of the VAD enhanced residents' performance in simulation.

Gepubliceerd: Plast Reconstr Surg. 2023.
Impact factor: 3.6 ; Q1

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5. Facilitating direct patient access to safety information about their breast implant: A Patient Access Tool sourced by the Dutch Breast Implant Registry
Harmeling JX, Bruins TA, Becherer BE, Hoornweg MJ, Harmsen M, Mureau MAM, Rakhorst HA.

Gepubliceerd: J Plast Reconstr Aesthet Surg. 2023;80:190-2.
Impact factor: 2.7 ; Q2

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6. Reoperation After Operative Treatment of Open Finger Fractures
Oflazoglu K, Smits LJH, Rakhorst H, Eberlin KR, Ritt M, Chen NC.

Background: Our primary aim was to develop a prediction model for return to the operating room (OR) after open finger fractures by studying the reoperation rate of open finger fractures based on patient demographics, injury mechanism, injury severity, and type of initial surgical fixation. The secondary aim was to study the predictors for secondary surgery due to nonunion, postoperative infection, and secondary amputation.
Methods: In the retrospective chart review, 1321 open finger fractures of 907 patients were included. Demographic-, injury-, and treatment-related factors were gathered from medical records.
Results: We found that open fractures involving the thumb had lower odds of undergoing secondary surgery. Crush injury, proximal phalangeal fracture, arterial injury, other injured fingers, and other injuries to the ipsilateral hand were associated with higher odds of undergoing secondary surgery. However, the associated factors we identified were not powerful enough to create a predictive model. Other injury to the ipsilateral hand, vein repair, and external fixator as initial treatment were associated with postoperative nonunion. Crush injury and proximal phalangeal fracture were associated with postoperative infection. No factors were associated with secondary amputation.
Conclusions: A quarter of open finger fractures will likely need more than one surgical procedure, especially in more severely injured fingers, due to crush or with vascular impairment. Furthermore, fractures involving the thumb have less reoperation, while fractures involving the proximal phalanx have poorest outcomes.

Gepubliceerd: Hand (N Y). 2023;18(7):1111-9.

Impact factor: onbekend

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7. A Threshold QuickDASH Score for Estimating a Diagnosis of Major Depression in Patients With Fingertip Injuries in the American and Dutch Population
Oflazoglu K, Verheul EM, Pong TM, Ritt M, Rakhorst H, Chen NC.

Background: The aim was to determine the threshold Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) score that estimates a diagnosis of major depression in patients with fingertip injuries in American and Dutch patients.
Methods: In this observational cross-sectional study, 112 patients with a recent fingertip injury measured symptoms of depression with the Patient Health Questionnaire and upper extremity disability with the QuickDASH.
Results: In the US cohort, 8 of 56 patients had an estimated diagnosis of major depression. A threshold value of QuickDASH of 50 showed a sensitivity of 88% and a specificity of 81%, with a negative predicting value (NPV) of 95% for an estimated diagnosis of major depression. In the Dutch cohort, 7 of 56 patients had an estimated diagnosis of major depression. The same threshold score of 50 had a sensitivity of 71%, a specificity of 63%, and an NPV of 94%.
Conclusions: We have found a correlation between experienced loss of function and an estimated diagnosis of major depression in patients with a fingertip injury. Referral to the primary care physician for further evaluation of depression in these patients is advised.

Gepubliceerd: Hand (N Y). 2023;18(4):692-700.
Impact factor: onbekend

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8. Effect of Total Breast Reconstruction With Autologous Fat Transfer Using an Expansion Device vs Implants on Quality of Life Among Patients With Breast Cancer: A Randomized Clinical Trial
Piatkowski AA, Wederfoort JLM, Hommes JE, Schop SSJ, Krastev TK, van Kuijk SMJ, van der Hulst R, BREAST Trial Investigators: Rakhorst H.

Importance: There is a need for a new, less invasive breast reconstruction option for patients who undergo mastectomy in their breast cancer treatment.
Objective: To investigate quality of life (QoL) among patients undergoing a new breast reconstruction technique, autologous fat transfer (AFT), compared with that among patients undergoing implant-based reconstruction (IBR).
Design, setting, and participants: The BREAST trial was a randomized clinical trial conducted between November 2, 2015, and October 31, 2021, performed in 7 hospitals across the Netherlands. Follow-up was 12 months. Referrals could be obtained from general practitioners and all departments from participating or nonparticipating hospitals. The patients with breast cancer who had undergone mastectomy and were seeking breast reconstruction were screened for eligibility (radiotherapy history and physique) by participating plastic surgeons. Patients receiving postmastectomy radiotherapy were excluded.
Interventions: Breast reconstruction with AFT plus expansion or 2-phased IBR. Randomization was done in a 1:1 ratio.
Main outcomes and measures: The statistical analysis was performed per protocol. The predefined primary outcome was QoL at 12 months after final surgery. This was measured by the BREAST-Q questionnaire, a validated breast reconstruction surgery questionnaire. Questions on the BREAST-Q questionnaire are scored from 0 to 100, with a higher score indicating greater satisfaction or better QoL (depending on the scale). Secondary outcomes were breast volume and the safety and efficacy of the techniques.

Results: A total of 193 female patients (mean [SD] age, 49.2 [10.6] years) 18 years or older who desired breast reconstruction were included, of whom 91 patients in the AFT group (mean [SD] age, 49.3 [10.3] years) and 80 in the IBR group (mean age, 49.1 [11.0] years) received the allocated intervention. In total, 64 women in the AFT group and 68 women in the IBR group completed follow-up. In the IBR group, 18 patients dropped out mainly due to their aversion to implant use while in the AFT group 6 patients ended their treatment prematurely because of the burden (that is, the treatment being too heavy or tiring). The BREAST-Q scores were higher in the AFT group in all 5 domains and significantly higher in 3: satisfaction with breasts (difference, 9.9; P = .002), physical well-being: chest (difference; 7.6; P = .007), and satisfaction with outcome (difference, 7.6; P = .04). Linear mixed-effects regression analysis showed that QoL change over time was dependent on the treatment group in favor of AFT. The mean (SD) breast volume achieved differed between the groups (AFT: 300.3 [111.4] mL; IBR: 384.1 [86.6] mL). No differences in oncological serious adverse events were found.
Conclusions and relevance: This randomized clinical trial found higher QoL and an increase in QoL scores over time in the AFT group compared with the IBR group. No evidence was found that AFT was unsafe. This is encouraging news since it provides a third, less invasive reconstruction option for patients with breast cancer.

Gepubliceerd: JAMA Surg. 2023;158(5):456-64.
Impact factor: 16.9 ; Q1

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9. Reconstruction of Noma Sequelae: A Surgical Treatment Algorithm Developed from Lessons from 210 Cases in Ethiopia
Rakhorst HA, Gresnigt TM, van Kooten O, Nishikawa H, Fourie L, Mizen KD.

Noma is an infectious disease affecting mostly children aged 0-10. Although it has almost completely disappeared from the Western world, it is still prevalent in many developing regions, mainly Africa's Sahel region. The infection behaves like a necrotizing fasciitis of the face, originating from the gums and progressively expanding into the cheek, nose, or eye regions. In an estimated 90% of cases, the disease is lethal as a result of systemic sepsis. For survivors, typical results are extensive defects of the cheek, nose, and periorbital and perioral regions. Due to the defects, extensive scarring is common, which leads to secondary problems such as growth alterations in an infant's skeleton due to inhibition and restraint of growth resulting typically in cicatricial skeletal hypoplasia. Other sequelae include trismus, partially caused by scarring or complete fusion between maxilla/zygomatic arch and mandible. The resulting overall disfiguring facial appearance results in patients being disabled and socially isolated. METHODS: Facing Africa is a UK-based non-governmental organization that treats the secondary problems of Ethiopian noma survivors. Operations are performed in Addis Ababa by a visiting expert team. Postoperatively, patients are seen annually for years after the surgery. RESULTS: This article discusses basic principles, goals, and a practical surgical algorithm for operating on lip, cheek, and oral defects, based on 210 noma patients who were operated on in Ethiopia over a period of 11 years. CONCLUSIONS: The suggested algorithm has proven to work for the Facing Africa team members and is considered shareware for all surgeons to use and benefit from.

Gepubliceerd: Plast Reconstr Surg Glob Open. 2023;11(3):e4844.
Impact factor: 1.5 ; Q onbekend

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10. The Areola study: design and rationale of a cohort study on long-term health outcomes in women with implant-based breast reconstructions

Spoor J, Mureau MAM, Hommes J, Rakhorst H, Dassen AE, Oldenburg HSA, Vissers YLJ, Heuts EM, Koppert LB, Zaal LH, van der Hulst R, Vrancken Peeters M, Bleiker EMA, van Leeuwen FE.

Background: Implant-based breast reconstructions contribute considerably to the quality of life of breast cancer patients. A knowledge gap exists concerning the potential role of silicone breast implants in the development of so-called "breast implant illness" (BII) and autoimmune diseases in breast cancer survivors with implant-based reconstructions. BII is a constellation of non-specific symptoms reported by a small group of women with silicone breast implants.
Methods: The Areola study is a multicenter retrospective cohort study with prospective follow-up aiming to assess the risk of BII and autoimmune diseases in female breast cancer survivors with and without silicone breast implants. In this report, we set out the rationale, study design, and methodology of this cohort study. The cohort consists of breast cancer survivors who received surgical treatment with implant-based reconstruction in six major hospitals across the Netherlands in the period between 2000 and 2015. As a comparison group, a frequency-matched sample of breast cancer survivors without breast implants will be selected. An additional group of women who received breast augmentation surgery in the same years will be selected to compare their characteristics and health outcomes with those of breast cancer patients with implants. All women who are still alive will be invited to complete a web-based questionnaire covering health-related topics. The entire cohort including deceased women will be linked to population-based databases of Statistics Netherlands. These include a registry of hospital diagnostic codes, a medicines prescription registry, and a cause-of-death registry, through which diagnoses of autoimmune diseases will be identified. Outcomes of interest are the prevalence and incidence of BII and autoimmune diseases. In addition, risk factors for the development of BII and autoimmune disorders will be assessed among women with implants.
Discussion: The Areola study will contribute to the availability of reliable information on the risks of BII and autoimmune diseases in Dutch breast cancer survivors with silicone breast implants. This will inform breast cancer survivors and aid future breast cancer patients and their treating physicians to make informed decisions about reconstructive strategies after mastectomy.
Registration: This study is registered at ClinicalTrials.gov on June 2, 2022 (NCT05400954).

Gepubliceerd: Ann Epidemiol. 2023;82:16-25.
Impact factor: 5.6 ; Q1

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11. SCI-QOL and WOUND-Q Have the Best Patient-reported Outcome Measure Design: A Systematic Literature Review of PROMs Used in Chronic Wounds
van Alphen TC, Ter Brugge F, van Haren E, Hoogbergen MM, Rakhorst H.

Chronic wounds are a significant burden on healthcare systems due to high costs of care (2%-4% total healthcare cost) and a considerable burden on patient's quality of life. Patient-reported outcome measures (PROMs) are questionnaires developed to enable patient self-assessments of their outcomes. A gap in knowledge exists because previous reviews on wound-specific PROMs did not evaluate the quality of the development. The main question is which PROM has the best quality development properties and should be used in clinical care and research. METHODS: PubMed, Embase, and CINAHL were searched from their inception through December 2021. Studies that included patients aged 18 years or older, with chronic wounds, and who reported using a condition-specific PROM for wounds were extracted. We excluded generic PROMs, comments, guidelines, and editorial letters. The COSMIN-guidelines were used to evaluate the quality of the PROMs. RESULTS: Of the 16,356 articles, a total of 251 articles describing 33 condition-specific PROMs for wounds were used. In total, 17 of 33 (52%) PROMs were developed for specific wound types, and nine of 33 (27%) PROMs were developed for any type of wound. Two of 33 (6%) PROMs were not rated because no development article was available. Only the SCI-QOL (Spinal Cord Injury-QOL) and the WOUND-Q

rated "very good" in PROM design. CONCLUSIONS: Thirty-three condition-specific PROMs were found. Only the SCI-QOL and the WOUND-Q rated very good in PROM design. The WOUND-Q is the only condition-specific PROM, which can be used in all types of chronic wounds in any anatomic location.

Gepubliceerd: Plast Reconstr Surg Glob Open. 2023;11(1):e4723.
Impact factor: 1.5 ; Q onbekend

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12. The Mandatory German Breast Implant Registry Law: A Model for Sustainable Implant Registries
von Fritschen U, Rakhorst HA, Stark B, Ahern S, Prantl L, Fricke A.

Background: Recurrent scandals involving breast implants have revealed that scientific evidence on the performance of these devices is lacking, and passive monitoring systems are not capable of detecting problems at an early stage. The German health authorities therefore decided to implement a prospective, mandatory registry.
Objectives: The aim of this article was to provide information about the advantages of implementing a mandatory registry, the potential hurdles involved, and to establish structural requirements that future registries can use.
Methods: Since 2018, the authors have assisted the German Ministry of Health in refining the Implant Law and its implementation. They adapted an internationally consented dataset, promoted international data amplification and conducted monthly trial inputs for over 2 years. By identifying several key issues they were able to assist in developing solutions.
Results: The cooperation with the authorities was characterized by appreciation of the authors' expertise and previous international work. Challenges included data privacy issues, federal competence, longitudinal follow-up, and contact data; as well as associated costs and technical solutions for data inclusion and the use of information technology to communicate with stakeholders. Addressing these challenges required considerable interference with personal rights and complementary measures for all stakeholders. Extensive structural precautions were taken to safeguard personal data privacy as far as possible.
Conclusions: The authors' experience and lessons learned can guide registries seeking to engage in high levels of evidence data. The authors describe their approach, the obstacles they encountered, and the strategies employed to overcome the setbacks of other registries.

Gepubliceerd: Aesthet Surg J. 2023;43(11):Np858-np65.
Impact factor: 3.1 ; Q1

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13. Risk factors for unplanned reoperation during the expansion phase in two-stage breast reconstruction in the Dutch Breast Implant Registry
Vrolijk JJ, Bargon CA, Becherer BE, Wilschut JA, van Bommel ACM, Hommes JE, Keuter XHA, Young-Afat DA, Verkooijen HM, van der Hulst R, Mureau MAM, Rakhorst HA.

Background: The majority of postmastectomy breast reconstructions (PMBRs) are currently performed in two stages using a tissue expander (TE). However, complications during the expansion phase occur regularly, leading to unplanned reoperations and/or reconstruction failure. This study aimed to identify risk factors for unplanned reoperation after TE placement, assessed the time until unplanned and planned reoperation, and investigated indications for unplanned reoperation.
Methods: Patient and surgery-related characteristics of patients who underwent two-stage PMBR between 2017 and 2021 were collected from the Dutch Breast Implant Registry (DBIR). Unplanned

reoperation was defined as TE explantation followed by either no replacement or replacement with the same or a different TE. Co-variate adjusted characteristics associated with unplanned reoperation were determined using backward stepwise selection and multivariable logistic regression analyses.
Results: In total, 2529 patients (mean age, 50.2 years) were included. Unplanned reoperation occurred in 19.4 percent of all registered TEs (n=3190). Independent factors associated with unplanned reoperation were BMI≥25 kg/m 2 (adjusted Odds Ratio [aOR]=1.63;99% Confidence Interval [99%CI]=1.20-2.57 for BMI 25-29.9 kg/m2, aOR=2.57;99%CI=1.74-3.78 for BMI≥30 kg/m 2), low institutional volume (aOR=1.51;99%CI=1.06-2.18), no drains (aOR=2.06;99%CI=1.15-3.60), subcutaneous TE placement (aOR=5.71;99%CI=3.59-9.10), and partial pectoralis major muscle coverage (aOR=1.35;99%CI=1.02-1.79). Age<40 years (aOR=0.49;99%CI=0.32-0.74) and delayed PMBR (aOR=0.35;99%CI=0.19-0.60) reduced the risk of unplanned reoperation. Median time until reoperation was 97 days for unplanned and 213 days for planned reoperation. Deep wound infections were most often registered as indication for unplanned reoperation (34.4 percent).
Conclusion: This study identified several risk factors for unplanned reoperation which may be used to reduce complications in expander-based PMBR.

Gepubliceerd: Plast Reconstr Surg. 2023.
Impact factor: 3.6 ; Q1

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14. Ensuring access to post-cancer breast reconstructions: COVID-19 lessons from the Dutch Breast Implant Registry
Vrolijk JJ, Young-Afat DA, Mureau MAM, Rakhorst HA, van Bommel ACM, Hoornweg MJ.

Background: COVID-19 has impacted breast implant surgery for oncological and non-oncological patients worldwide. This population-based study aimed to evaluate the impact of the COVID-19 pandemic on access to reconstructive and cosmetic breast implant surgery in the Netherlands using real-world data to describe trends, and to identify lessons to prevent future capacity problems within (inter)national healthcare.
Methods: This longitudinal study included patients undergoing breast implant surgery from the mandatory nationwide Dutch Breast Implant Registry. For 2020, the first COVID-19 wave, intermediate period, and second wave were defined. We compared data from during the pandemic to a pre-pandemic (2019) reference year, assessing differences in the number of registered breast implants, and patient and surgery-related characteristics.
Results: A total of 34133 breast implants (17459 patients) were included. Compared to 2019, fewer implants were registered for post-cancer (n=484; -14.7%), cosmetic (n=480; -3.6%), and gender-affirming indications (n=104; -38.0%) during 2020. Fewer implants were registered in academic (n=196; -22.0%) and regional hospitals (n=1591; -16.5%), but more in private clinics (n=725; +10.1%). After the first wave, up to twice as many implants were registered in private clinics compared to 2019. No differences were found in characteristics of patients undergoing surgery in 2020 versus 2019.
Conclusion: Hospital-based reconstructive and gender-affirming surgery were heavily impacted during the pandemic, while private-clinic-based cosmetic surgery quickly recovered. These outcomes are useful to fuel discussions about how healthcare could be reorganized in times of capacity problems. We suggest exploring options to deploy private clinics for ambulatory surgery aiming to keep hospital capacity available for acutely ill patients.

Gepubliceerd: Eur J Surg Oncol. 2023;49(9):106984.
Impact factor: 3.8 ; Q1

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15. Aesthetic Evaluation of Breast Reconstruction with Autologous Fat Transfer vs. Implants
Wederfoort JLM, Kleeven A, Hommes JE, Van Kuijk SMJ, van der Hulst R, Piatkowski A, BREAST Trial Investigators: Rakhorst H.

Background: Autologous fat transfer (AFT) seems to be a new minimal invasive method for total breast reconstruction, yet how patients, surgeons, and laymen evaluate cosmesis is lacking. The aim of this study was to evaluate the aesthetic outcome of AFT (intervention group) for total breast reconstruction post-mastectomy, as compared to implant-based reconstruction (IBR) (control group).
Methods: A random and blinded 3D photographic aesthetic outcome study was performed on a selection of 50 patients, scored by three panels: plastic surgeons, breast cancer patients, and laymen. Secondary outcomes included agreement within groups and possible patient characteristics influencing scoring.
Results: Breast cancer patients and plastic surgeons did not differ in the aesthetic scores between the treatment groups. In contrast, the laymen group scored AFT patients lower than IBR patients (- 1.04, $p < 0.001$). Remarkably, mean given scores were low for all groups and overall agreement within groups was poor (ICC < 0.50). Higher scores were given when subjects underwent a bilateral reconstruction and if a mamilla was present.
Conclusion: Evaluation of aesthetic outcomes varies greatly. Hence, aesthetic outcome remains a very personal measure and this emphasizes the importance of thorough patient counseling including information on achievable aesthetic results before starting a reconstructive procedure.
Level of evidence iii: This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

Gepubliceerd: Aesthetic Plast Surg. 2023;47(2):593-604.
Impact factor: 2.4 ; Q2

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17. Donor Site Satisfaction Following Autologous Fat Transfer for Total Breast Reconstruction
Wederfoort JLM, van Santbrink E, Hommes JE, Heuts EM, Van Kuijk SMJ, van der Hulst R, Piatkowski A, BREAST Trial Investigators: Rakhorst H.

Background: With evolving breast cancer survival and patient preferences, it is essential that reconstructive surgeons worldwide continue searching for the best reconstruction technique for patients. Autologous fat transfer (AFT) is a relatively new technique for total breast reconstruction that has already proven to be effective and safe with all advantages of autologous tissue. However, little is known about the aesthetic results and satisfaction concerning donor sites.
Objectives: The aim of this study was to measure donor site satisfaction following AFT for total breast reconstruction in breast cancer patients.
Methods: Between May and August of 2021, participants of the BREAST- trial who were at least 24 months after their final reconstruction surgery were invited to complete an additional survey concerning donor sites. The BODY-Q was utilized for data collection. Results of AFT patients were compared with a control group of implant-based reconstruction patients who did not have a donor site.
Results: A total of 51 patients (20 control, 31 intervention) completed the questionnaire. Satisfaction with body did not statistically differ between the groups. The most frequent complaint was contour irregularities (31 reports, 60.8%), with the least favorable donor site being thighs (23 reports, 53.5%) in the AFT group.
Conclusions: Satisfaction with body did not differ between breast cancer patients receiving AFT or implant-based reconstruction, meaning that large-volume liposuction does not aesthetically affect the utilized donor sites. Nevertheless, reconstructive surgeons should be aware of possible donor site complications, especially contour irregularities at the thighs, and discuss this with their patients.

Gepubliceerd: Aesthet Surg J. 2023;43(1):40-8.
Impact factor: 3.1 ; Q1

Totale impact factor: 59.5
Gemiddelde impact factor: 3.7

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 8
Totale impact factor: 20.5
Gemiddelde impact factor: 2.6

Raad van Bestuur

1. Development of machine learning models to predict cancer-related fatigue in Dutch breast cancer survivors up to 15 years after diagnosis
Beenhakker L, Wijlens KAE, Witteveen A, Heins M, Korevaar JC, de Ligt KM, Bode C, Vollenbroek-Hutten MMR, Siesling S.

Purpose: To prevent (chronic) cancer-related fatigue (CRF) after breast cancer, it is important to identify survivors at risk on time. In literature, factors related to CRF are identified, but not often linked to individual risks. Therefore, our aim was to predict individual risks for developing CRF.
Methods: Two pre-existing datasets were used. The Nivel-Primary Care Database and the Netherlands Cancer Registry (NCR) formed the Primary Secondary Cancer Care Registry (PSCCR). NCR data with Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES) data resulted in the PSCCR-PROFILES dataset. Predictors were patient, tumor and treatment characteristics, and pre-diagnosis health. Fatigue was GP-reported (PSCCR) or patient-reported (PSCCR-PROFILES). Machine learning models were developed, and performances compared using the C-statistic.
Results: In PSCCR, 2224/12813 (17%) experienced fatigue up to 7.6 ± 4.4 years after diagnosis. In PSCCR-PROFILES, 254 (65%) of 390 patients reported fatigue 3.4 ± 1.4 years after diagnosis. For both, models predicted fatigue poorly with best C-statistics of 0.561 ± 0.006 (PSCCR) and 0.669 ± 0.040 (PSCCR-PROFILES).
Conclusion: Fatigue (GP-reported or patient-reported) could not be predicted accurately using available data of the PSCCR and PSCCR-PROFILES datasets.
Implications for cancer survivors: CRF is a common but underreported problem after breast cancer. We aimed to develop a model that could identify individuals with a high risk of developing CRF, ideally to help them prevent (chronic) CRF. As our models had poor predictive abilities, they cannot be used for this purpose yet. Adding patient-reported data as predictor could lead to improved results. Until then, awareness for CRF stays crucial.

Gepubliceerd: J Cancer Surviv. 2023.
Impact factor: 3.7 ; Q1

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2. Validity and reliability of Eforto®, a system to (self-)monitor grip strength and muscle fatigability in older persons
De Dobbeleer L, Swart MM, Geerds MAJ, Baggen RJ, Jansen AS, Tielemans R, Silva H, Lieten S, Barbé K, Peeters G, Vollenbroek-Hutten MMR, Melis RJF, Bautmans I.

Introduction: We developed Eforto®, an innovative system for (self-)monitoring of grip strength (GS) and muscle fatigability (Fatigue Resistance (FR = time until GS decreased to 50% of maximum during sustained contraction) and grip work (GW = area under the strength-time curve)). The Eforto® system consists of a rubber bulb that is wirelessly connected to a smartphone-based application, and a telemonitoring platform. The aim was to evaluate the validity and reliability of Eforto® to measure muscle fatigability.
Methods: Community-dwelling older persons (n = 61), geriatric inpatients (n = 26) and hip fracture patients (n = 25) were evaluated for GS and muscle fatigability. In community dwellers fatigability was tested twice in the clinic (once with Eforto®, once with Martin Vigorimeter (MV), standard analog handgrip system) and for six consecutive days as a self-assessment at home with Eforto®. In hospitalized participants, fatigability was tested twice using Eforto®, once by a researcher and once by a health professional.

Results: Criterion validity was supported by good to excellent correlations between Eforto® and MV for GS (r = 0.95) and muscle fatigability (FR r = 0.81 and GW r = 0.73), and no significant differences in measurements between both systems. Inter-rater and intra-rater reliability for GW were moderate to excellent (intra-class correlation: 0.59-0.94). The standard error of measurement for GW was small for geriatric inpatients and hip fracture patients (224.5 and 386.5 kPa*s) and higher for community-dwellers (661.5 kPa*s).
Discussion/conclusion: We established the criterion validity and reliability of Eforto® in older community-dwelling persons and hospitalized patients, supporting the implementation of Eforto® for (self-)monitoring of muscle fatigability.

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Impact factor: 4.0 ; Q2

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3. A Digital Lifestyle Coach (E-Supporter 1.0) to Support People With Type 2 Diabetes: Participatory Development Study
Hietbrink EAG, Middelweerd A, van Empelen P, Preuhs K, Konijnendijk AAJ, Oude Nijeweme-d'Hollosy W, Schrijver LK, Laverman GD, Vollenbroek-Hutten MMR.

Background: A healthy lifestyle, including regular physical activity and a healthy diet, is becoming increasingly important in the treatment of chronic diseases. eHealth interventions that incorporate behavior change techniques (BCTs) and dynamic tailoring strategies could effectively support a healthy lifestyle. E-Supporter 1.0 is an eCoach designed to support physical activity and a healthy diet in people with type 2 diabetes (T2D).
Objective: This paper aimed to describe the systematic development of E-Supporter 1.0.
Methods: Our systematic design process consisted of 3 phases. The definition phase included the selection of the target group and formulation of intervention objectives, and the identification of behavioral determinants based on which BCTs were selected to apply in the intervention. In the development phase, intervention content was developed by specifying tailoring variables, intervention options, and decision rules. In the last phase, E-Supporter 1.0 integrated in the Diameter app was evaluated using a usability test in 9 people with T2D to assess intervention usage and acceptability.
Results: The main intervention objectives were to stimulate light to moderate-vigorous physical activities or adherence to the Dutch dietary guidelines in people with T2D. The selection of behavioral determinants was informed by the health action process approach and theories explaining behavior maintenance. BCTs were included to address relevant behavioral determinants (eg, action control, self-efficacy, and coping planning). Development of the intervention resulted in 3 types of intervention options, consisting of motivational messages, behavioral feedback, and tailor-made supportive exercises. On the basis of IF-THEN rules, intervention options could be tailored to, among others, type of behavioral goal and (barriers to) goal achievement. Data on these variables could be collected using app data, activity tracker data, and daily ecological momentary assessments. Usability testing revealed that user experiences were predominantly positive, despite some problems in the fixed delivery of content.
Conclusions: The systematic development approach resulted in a theory-based and dynamically tailored eCoach. Future work should focus on expanding intervention content to other chronic diseases and lifestyle behaviors, enhancing the degree of tailoring and evaluating intervention effects on acceptability, use, and cost-effectiveness.

Gepubliceerd: JMIR Hum Factors. 2023;10:e40017.
Impact factor: 2.7 ; Q onbekend

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4. A Digital Coach (E-Supporter 1.0) to Support Physical Activity and a Healthy Diet in People With Type 2 Diabetes: Acceptability and Limited Efficacy Testing
Hietbrink EAG, Oude Nijeweme-d'Hollosy W, Middelweerd A, Konijnendijk AAJ, Schrijver LK, Ten Voorde AS, Fokkema EMS, Laverman GD, Vollenbroek-Hutten MMR.

Background: A healthy lifestyle, including regular physical activity and a healthy diet, is increasingly part of type 2 diabetes (T2D) management. As many people with T2D have difficulty living and maintaining a healthy lifestyle, there is a need for effective interventions. eHealth interventions that incorporate behavior change theories and tailoring are considered effective tools for supporting a healthy lifestyle. The E-Supporter 1.0 digital coach contains eHealth content for app-based eHealth interventions and offers tailored coaching regarding physical activity and a healthy diet for people with T2D.
Objective: This study aimed to assess the acceptability of E-Supporter 1.0 and explore its limited efficacy on physical activity, dietary behavior, the phase of behavior change, and self-efficacy levels.
Methods: Over a span of 9 weeks, 20 individuals with T2D received daily motivational messages and weekly feedback derived from behavioral change theories and determinants through E-Supporter 1.0. The acceptability of the intervention was assessed using telephone-conducted, semistructured interviews. The interview transcripts were coded using inductive thematic analysis. The limited efficacy of E-Supporter 1.0 was explored using the Fitbit Charge 2 to monitor step count to assess physical activity and questionnaires to assess dietary behavior (using the Dutch Healthy Diet index), phase of behavior change (using the single-question Self-Assessment Scale Stages of Change), and self-efficacy levels (using the Exercise Self-Efficacy Scale).
Results: In total, 5 main themes emerged from the interviews: perceptions regarding remote coaching, perceptions regarding the content, intervention intensity and duration, perceived effectiveness, and overall appreciation. The participants were predominantly positive about E-Supporter 1.0. Overall, they experienced E-Supporter 1.0 as a useful and easy-to-use intervention to support a better lifestyle. Participants expressed a preference for combining E-Supporter with face-to-face guidance from a health care professional. Many participants found the intensity and duration of the intervention to be acceptable, despite the coaching period appearing relatively short to facilitate long-term behavior maintenance. As expected, the degree of tailoring concerning the individual and external factors that influence a healthy lifestyle was perceived as limited. The limited efficacy testing showed a significant improvement in the daily step count (z=-2.040; P=.04) and self-efficacy levels (z=-1.997; P=.046) between baseline and postintervention. Diet was improved through better adherence to Dutch dietary guidelines. No significant improvement was found in the phase of behavior change (P=.17), as most participants were already in the maintenance phase at baseline.
Conclusions: On the basis of this explorative feasibility study, we expect E-Supporter 1.0 to be an acceptable and potentially useful intervention to promote physical activity and a healthy diet in people with T2D. Additional work needs to be done to further tailor the E-Supporter content and evaluate its effects more extensively on lifestyle behaviors.

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Impact factor: 2.2 ; Q onbekend

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5. Transparency in hip fracture recovery over institutional boundaries: The transmural monitoring pathway
Nijmeijer WS, van Dartel D, de Groot R, Woudsma S, Folbert EC, den Braber N, Vermeer M, Hegeman JH, Vollenbroek-Hutten MM.

Objectives: To develop a transmural pathway for healthcare professionals across institutions to monitor the recovery of hip fracture patients. The secondary objectives were to evaluate the pathway's feasibility and initial outcomes.
Design: Prospective cohort study.
Method: Stakeholders of the hospital and geriatric rehabilitation institutions implemented a transmural monitoring pathway in which different geriatric health domains were monitored during three phases: The in-hospital, inpatient rehabilitation, and outpatient follow-up phase. The outcomes for the first 291 patients and the feasibility of the pathway were evaluated. If the outcomes of the clinimetrics significantly improved over time, progress in functional recovery was assumed. Feasibility was assessed according to the rate of adherence to the clinimetric tests.
Results: During the in-hospital phase, patients showed a decline in functional level (the Katz index of independence in Activities of Daily Living (Katz-ADL) pre-fracture vs. discharge: 0 (0-2) vs. 4 (4-5), $P < 0.001$). Patients, in which 78.6% (n = 140) had cognitive impairment and 41.2% had malnutrition, showed the most progress (Katz-ADL 2 (1-3)) during the inpatient rehabilitation phase. In the outpatient follow-up phase, recovery remained ongoing, but most patients had not returned to their pre-fracture functional levels (Katz-ADL 1 (1-3)). The pathway feasibility during the first phase was excellent (>85%), whereas room for improvement existed during other phases (<85%).
Conclusion: The transmural monitoring pathway provides insight into the entire recovery process for all involved healthcare professionals. Patients showed the most progress during the rehabilitation phase. The pathway feasibility was excellent during the in-hospital phase, but improvements could be made during other phases.

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Impact factor: 3.0 ; Q1

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6. The prediction of early mortality following hip fracture surgery in patients aged 90 years and older: the Almelo Hip Fracture Score 90 (AHFS(90))
Nijmeijer WS, Voorthuis BJ, Groothuis-Oudshoorn CGM, Würdemann FS, van der Velde D, Vollenbroek-Hutten MMR, Hegeman JH.

The AHFS(90) was developed for the prediction of early mortality in patients ≥ 90 years undergoing hip fracture surgery. The AHFS(90) has a good accuracy and in most risk categories a good calibration. In our study population, the AHFS(90) yielded a maximum prediction of early mortality of 64.5%. PURPOSE: Identifying hip fracture patients with a high risk of early mortality after surgery could help make treatment decisions and information about the prognosis. This study aims to develop and validate a risk score for predicting early mortality in patients ≥ 90 years undergoing hip fracture surgery (AHFS(90)). METHODS: Patients ≥ 90 years, surgically treated for a hip fracture, were included. A selection of possible predictors for mortality was made. Missing data were subjected to multiple imputations using chained equations. Logistic regression was performed to develop the AHFS(90), which was internally and externally validated. Calibration was assessed using a calibration plot and comparing observed and predicted risks. RESULTS: One hundred and two of the 922 patients (11.1%) died ≤ 30 days following hip fracture surgery. The AHFS(90) includes age, gender, dementia, living in a nursing home, ASA score, and hemoglobin level as predictors for early mortality. The AHFS(90) had good accuracy (area under the curve 0.72 for geographic cross validation). Predicted risks correspond with observed risks of early mortality in four risk categories. In two risk categories, the AHFS(90) overestimates the risk. In one risk category, no mortality was observed; therefore, no analysis was possible. The AHFS(90) had a maximal prediction of early mortality of 64.5% in this study population. CONCLUSION: The AHFS(90) accurately predicts early mortality after hip fracture surgery in patients ≥ 90 years of age. Predicted risks correspond to observed risks in most risk categories. In our study population, the AHFS(90) yielded a maximum prediction of early mortality of 64.5%.

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Impact factor: 4.0 ; Q2

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7. Patterns of physical activity over time in older patients rehabilitating after hip fracture surgery: a preliminary observational study
van Dartel D, Wang Y, Hegeman JH, Vermeer M, Vollenbroek-Hutten MMR.

Background: To investigate patterns of continuously monitored physical activity in older patients rehabilitating after hip fracture surgery and the association with patient characteristics.
Methods: Physical activity of surgically treated hip fracture patients aged 70 years or older, who were rehabilitating at a skilled nursing home, was continuously monitored using a tri-axial accelerometer. The intensity of physical activity per day was calculated from the accelerometer signals to describe the daily physical activity levels of the enrolled patients. The patterns of three different aspects of physical activity were investigated: overall physical activity, overall variability, and day-to-day variability. Two experts in the geriatric rehabilitation field helped identifying unique physical activity patterns for each aspect based on visual analysis. Eighteen healthcare professionals independently classified each patient in one of the predefined patterns for each aspect. Differences between physical activity patterns and patient characteristics were assessed using a Kruskal-Wallis or Fisher's Exact Test.
Results: Physical activity data from 66 older patients were used in this preliminary study. A total of six unique patterns were identified for overall physical activity and overall variability, and five unique patterns for the day-to-day variability. The most common pattern found for the overall physical activity and day-to-day variability had a S-shape, which first slowly increased, then steeply increased, and subsequently flattened (n = 23, 34.8%). A N-shape pattern was found the most common pattern for overall variability, which first slowly increased, then steeply increased, then decreased and lastly increased (n = 14, 21.2%). The functionality at admission to rehabilitation, measured with the Barthel Index, and the duration of rehabilitation stay differed between the patterns of physical activity.
Conclusions: Multiple patterns of physical activity among older patients during hip fracture rehabilitation were found in this preliminary study. The functionality at admission to rehabilitation and the duration of rehabilitation stay were associated with the different patterns found in this study. Results of this study highlight the importance of personalized hip fracture treatment.

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Impact factor: 4.1 ; Q1

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8. Prediction of Physical Activity Patterns in Older Patients Rehabilitating After Hip Fracture Surgery: Exploratory Study
van Dartel D, Wang Y, Hegeman JH, Vollenbroek-Hutten MMR.

Background: Building up physical activity is a highly important aspect in an older patient's rehabilitation process after hip fracture surgery. The patterns of physical activity during rehabilitation are associated with the duration of rehabilitation stay. Predicting physical activity patterns early in the rehabilitation phase can provide patients and health care professionals an early indication of the duration of rehabilitation stay as well as insight into the degree of patients' recovery for timely adaptive interventions.
Objective: This study aims to explore the early prediction of physical activity patterns in older patients rehabilitating after hip fracture surgery at a skilled nursing home.
Methods: The physical activity of patients aged ≥70 years with surgically treated hip fracture was continuously monitored using an accelerometer during rehabilitation at a skilled nursing home.

Physical activity patterns were described in our previous study, and the 2 most common patterns were used in this study for pattern prediction: the upward linear pattern (n=15) and the S-shape pattern (n=23). Features from the intensity of physical activity were calculated for time windows with different window sizes of the first 5, 6, 7, and 8 days to assess the early rehabilitation moment in which the patterns could be predicted most accurately. Those features were statistical features, amplitude features, and morphological features. Furthermore, the Barthel Index, Fracture Mobility Score, Functional Ambulation Categories, and the Montreal Cognitive Assessment score were used as clinical features. With the correlation-based feature selection method, relevant features were selected that were highly correlated with the physical activity patterns and uncorrelated with other features. Multiple classifiers were used: decision trees, discriminant analysis, logistic regression, support vector machines, nearest neighbors, and ensemble classifiers. The performance of the prediction models was assessed by calculating precision, recall, and F_1-score (accuracy measure) for each individual physical activity pattern. Furthermore, the overall performance of the prediction model was calculated by calculating the F_1-score for all physical activity patterns together.
Results: The amplitude feature describing the overall intensity of physical activity on the first day of rehabilitation and the morphological features describing the shape of the patterns were selected as relevant features for all time windows. Relevant features extracted from the first 7 days with a cosine k-nearest neighbor model reached the highest overall prediction performance (micro F_1-score=1) and a 100% correct classification of the 2 most common physical activity patterns.
Conclusions: Continuous monitoring of the physical activity of older patients in the first week of hip fracture rehabilitation results in an early physical activity pattern prediction. In the future, continuous physical activity monitoring can offer the possibility to predict the duration of rehabilitation stay, assess the recovery progress during hip fracture rehabilitation, and benefit health care organizations, health care professionals, and patients themselves.

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Impact factor: onbekend

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9. Early Warning Scores to Support Continuous Wireless Vital Sign Monitoring for Complication Prediction in Patients on Surgical Wards: Retrospective Observational Study
van Rossum MC, Bekhuis REM, Wang Y, Hegeman JH, Folbert EC, Vollenbroek-Hutten MMR, Kalkman CJ, Kouwenhoven EA, Hermens HJ.

Background: Wireless vital sign sensors are increasingly being used to monitor patients on surgical wards. Although early warning scores (EWSs) are the current standard for the identification of patient deterioration in a ward setting, their usefulness for continuous monitoring is unknown.
Objective: This study aimed to explore the usability and predictive value of high-rate EWSs obtained from continuous vital sign recordings for early identification of postoperative complications and compares the performance of a sensor-based EWS alarm system with manual intermittent EWS measurements and threshold alarms applied to individual vital sign recordings (single-parameter alarms).
Methods: Continuous vital sign measurements (heart rate, respiratory rate, blood oxygen saturation, and axillary temperature) collected with wireless sensors in patients on surgical wards were used for retrospective simulation of EWSs (sensor EWSs) for different time windows (1-240 min), adopting criteria similar to EWSs based on manual vital signs measurements (nurse EWSs). Hourly sensor EWS measurements were compared between patients with (event group: 14/46, 30%) and without (control group: 32/46, 70%) postoperative complications. In addition, alarms were simulated for the sensor EWSs using a range of alarm thresholds (1-9) and compared with alarms based on nurse EWSs and single-parameter alarms. Alarm performance was evaluated using the sensitivity to predict complications within 24 hours, daily alarm rate, and false discovery rate (FDR).

Results: The hourly sensor EWSs of the event group (median 3.4, IQR 3.1-4.1) was significantly higher (P<.004) compared with the control group (median 2.8, IQR 2.4-3.2). The alarm sensitivity of the hourly sensor EWSs was the highest (80%-67%) for thresholds of 3 to 5, which was associated with alarm rates of 2 (FDR=85%) to 1.2 (FDR=83%) alarms per patient per day respectively. The sensitivity of sensor EWS-based alarms was higher than that of nurse EWS-based alarms (maximum=40%) but lower than that of single-parameter alarms (87%) for all thresholds. In contrast, the (false) alarm rates of sensor EWS-based alarms were higher than that of nurse EWS-based alarms (maximum=0.6 alarm/patient/d; FDR=80%) but lower than that of single-parameter alarms (2 alarms/patient/d; FDR=84%) for most thresholds. Alarm rates for sensor EWSs increased for shorter time windows, reaching 70 alarms per patient per day when calculated every minute.
Conclusions: EWSs obtained using wireless vital sign sensors may contribute to the early recognition of postoperative complications in a ward setting, with higher alarm sensitivity compared with manual EWS measurements. Although hourly sensor EWSs provide fewer alarms compared with single-parameter alarms, high false alarm rates can be expected when calculated over shorter time spans. Further studies are recommended to optimize care escalation criteria for continuous monitoring of vital signs in a ward setting and to evaluate the effects on patient outcomes.

Gepubliceerd: JMIR Perioper Med. 2023;6:e44483.
Impact factor: onbekend

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10. A holistic profile for cancer-related fatigue for women with breast cancer - a qualitative study
Wijlens KAE, Beenhakker L, Witteveen A, Siemerink EJM, Jansen L, Gernaat C, Schellekens MPJ, Siesling S, Vollenbroek-Hutten MMR, Bode C.

Objective: Cancer- related fatigue (CRF) is one of the most reported long-term effects after breast cancer and severely impacts quality of life. To come towards optimal treatment of multidimensional CRF, the first step is to use a holistic approach to develop a holistic patient profile including the patient's experience and impact of CRF on their life.
Methods and measures: Four semi- structured focus groups with twenty- seven breast cancer patients and fourteen interviews with healthcare professionals (HCPs) were held. Reflexive thematic analysis was used to define (sub)themes for the holistic patient profile. The themes of the interviews and focus groups were compared for validity.
Results: Breast cancer patients and HCPs described the same five major themes, consisting of experience of CRF, impact and consequences, coping, personality, and CRF treatment. Experience of CRF consists of cognitive, emotional, and physical aspects. Impact and consequences include work, family, partner relation, social contact and hobbies, body, and misunderstanding. Coping consists of twelve (mal)adaptive strategies. Personality and CRF treatment were summarised as themes.
Conclusions: A first holistic patient profile was introduced for CRF for breast cancer. This profile can be conceptualized into a questionnaire to collect information for personalized treatment recommendations and monitoring of CRF over time.

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Impact factor: 3.3 ; Q2

Totale impact factor: 27.0
Gemiddelde impact factor: 2.7

Aantal artikelen 1e, 2e of laatste auteur: 5
Totale impact factor: 12.0

Gemiddelde impact factor: 2.4

Radiologie

1. Validity of Early Outcomes as Indicators for Comparing Hospitals on Quality of Stroke Care
Amini M, Eijkenaar F, Lingsma HF, den Hartog SJ, Olthuis SGH, Martens J, van der Worp B, van Zwam W, van der Hoorn A, Roosendaal SD, Roozenbeek B, Dippel D, van Leeuwen N, MR CLEAN Registry Investigators: Brouwers P, Bulut T.

Background: Insight into outcome variation between hospitals could help to improve quality of care. We aimed to assess the validity of early outcomes as quality indicators for acute ischemic stroke care for patients treated with endovascular therapy (EVT).
Methods and Results: We used data from the MR CLEAN (Multicenter Randomized Controlled Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) Registry, a large multicenter prospective cohort study including 3279 patients with acute ischemic stroke undergoing EVT. Random effect linear and proportional odds regression were used to analyze the effect of case mix on between-hospital differences in 2 early outcomes: the National Institutes of Health Stroke Scale (NIHSS) score at 24 to 48 hours and the expanded thrombolysis in cerebral infarction score. Between-hospital variation in outcomes was assessed using the variance of random hospital effects (tau(2)). In addition, we estimated the correlation between hospitals' EVT-patient volume and (case-mix-adjusted) outcomes. Both early outcomes and case-mix characteristics varied significantly across hospitals. Between-hospital variation in the expanded thrombolysis in cerebral infarction score was not influenced by case-mix adjustment (tau (2)=0.17 in both models). In contrast, for the NIHSS score at 24 to 48 hours, case-mix adjustment led to a decrease in variation between hospitals (tau (2) decreases from 0.19 to 0.17). Hospitals' EVT-patient volume was strongly correlated with higher expanded thrombolysis in cerebral infarction scores (r=0.48) and weakly with lower NIHSS score at 24 to 48 hours (r=0.15).
Conclusions: Between-hospital variation in NIHSS score at 24 to 48 hours is significantly influenced by case-mix but not by patient volume. In contrast, between-hospital variation in expanded thrombolysis in cerebral infarction score is strongly influenced by EVT-patient volume but not by case-mix. Both outcomes may be suitable for comparing hospitals on quality of care, provided that adequate adjustment for case-mix is applied for NIHSS score.

Gepubliceerd: J Am Heart Assoc. 2023;12(8):e027647.
Impact factor: 5.4 ; Q2

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2. Thrombus imaging characteristics within acute ischemic stroke: similarities and interdependence
Arrarte Terreros N, Bruggeman AA, Kappelhof M, Tolhuisen ML, Brouwer J, Hoving JW, Konduri PR, van Kranendonk KR, Dutra BG, Alves HC, Dippel DW, van Zwam WH, Beenen LF, Yo LS, van Bavel E, Majoie CB, Marquering HA, MR CLEAN Registry Investigators: Brouwers P, Bulut T.

Background: The effects of thrombus imaging characteristics on procedural and clinical outcomes after ischemic stroke are increasingly being studied. These thrombus characteristics - for eg, size, location, and density - are commonly analyzed as separate entities. However, it is known that some of these thrombus characteristics are strongly related. Multicollinearity can lead to unreliable prediction models. We aimed to determine the distribution, correlation and clustering of thrombus imaging characteristics based on a large dataset of anterior-circulation acute ischemic stroke patients.
Methods: We measured thrombus imaging characteristics in the MR CLEAN Registry dataset, which included occlusion location, distance from the intracranial carotid artery to the thrombus (DT), thrombus length, density, perviousness, and clot burden score (CBS). We assessed intercorrelations with Spearman's coefficient (ρ) and grouped thrombi based on 1) occlusion location and 2) thrombus length, density and perviousness using unsupervised clustering.

Results: We included 934 patients, of which 22% had an internal carotid artery (ICA) occlusion, 61% M1, 16% M2, and 1% another occlusion location. All thrombus characteristics were significantly correlated. Higher CBS was strongly correlated with longer DT (ρ=0.67, p<0.01), and moderately correlated with shorter thrombus length (ρ=-0.41, p<0.01). In more proximal occlusion locations, thrombi were significantly longer, denser, and less pervious. Unsupervised clustering analysis resulted in four thrombus groups; however, the cohesion within and distinction between the groups were weak.
Conclusions: Thrombus imaging characteristics are significantly intercorrelated - strong correlations should be considered in future predictive modeling studies. Clustering analysis showed there are no distinct thrombus archetypes - novel treatments should consider this thrombus variability.

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Impact factor: 4.9 ; Q1

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3. Bifurcation occlusions and endovascular treatment outcome in acute ischemic stroke
Arrarte Terreros N, Bruggeman AAE, van Voorst H, Konduri PR, Jansen IGH, Kappelhof M, Tolhuisen ML, Boodt N, Dippel DWJ, van der Lugt A, van Zwam WH, van Oostenbrugge RJ, van der Worp HB, Emmer BJ, Meijer FJA, Roos Y, van Bavel E, Marquering HA, Majoie C, MR Clean Investigators: Brouwers P, Bulut T.

Background: A thrombus in the M1 segment of the middle cerebral artery (MCA) can occlude this main stem only or extend into the M1-M2 bifurcation. The occlusion pattern may affect endovascular treatment (EVT) success, as a bifurcated thrombus may be more prone to fragmentation during retrieval.
Objective: To investigate whether bifurcated thrombus patterns are associated with EVT procedural and clinical outcomes.
Methods: Occlusion patterns of MCA thrombi on CT angiography from MR CLEAN Registry patients were classified into three groups: main stem occlusion, bifurcation occlusion extending into one M2 branch, and bifurcation occlusion extending into both M2 branches. Procedural parameters, procedural outcomes (reperfusion grade and embolization to new territory), and clinical outcomes (24-48 hour National Institutes of Health Stroke Scale [$NIHSS_{FU}$] score, change in NIHSS scores between 24 and 48 hours and baseline Δ [NIHSS], and 90-day modified Rankin Scale [mRS] scores) were compared between occlusion patterns.
Results: We identified 1023 patients with an MCA occlusion of whom 370 (36%) had a main stem occlusion, 151 (15%) a single branch, and 502 (49%) a double branch bifurcation occlusion. There were no statistically significant differences in retrieval method, procedure time, number of retrieval attempts, reperfusion grade, and embolization to new territory between occlusion patterns. Patients with main stem occlusions had lower $NIHSS_{FU}$ scores than patients with single (7 vs 11, p=0.01) or double branch occlusions (7 vs 9, p=0.04). However, there were no statistically significant differences in Δ NIHSS or in 90-day mRS scores.
Conclusions: In our population, EVT procedural and long-term clinical outcomes were similar for MCA bifurcation occlusions and MCA main stem occlusions.

Gepubliceerd: J Neurointerv Surg. 2023;15(4):355-62.
Impact factor: 4.9 ; Q1

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4. Endovascular treatment for isolated posterior cerebral artery occlusion stroke in the MR CLEAN registry

Brouwer J, Ergezen S, Mulder M, Lycklama ANGJ, van Es A, van der Lugt A, Dippel DWJ, Majoie C, Roos Y, Coutinho JM, Emmer BJ, MR CLEAN Registry investigators: Brouwers P, Bulut T.

Background: Endovascular treatment (EVT) is standard of care in anterior circulation large vessel occlusions. In posterior circulation occlusions, data on EVT in isolated posterior cerebral artery (PCA) occlusions are limited, although PCA occlusions can cause severe neurological deficit.
Objective: To describe in a prospective study the clinical manifestations, outcomes, and safety of EVT in isolated PCA occlusions.
Methods: We used data (2014-2017) from the MR CLEAN Registry, a nationwide, prospective cohort of EVT-treated patients in the Netherlands. We included patients with acute ischemic stroke (AIS) due to an isolated PCA occlusion on CT angiography. Patients with concurrent occlusion of the basilar artery were excluded. Outcomes included change in National Institutes of Health Stroke Scale (ΔNIHSS) score, modified Rankin Scale (mRS) score 0-3 after 90 days, mortality, expanded Thrombolysis in Cerebral Infarction (eTICI), and periprocedural complications.
Results: Twenty (12%) of 162 patients with posterior circulation occlusions had an isolated PCA occlusion. Median age was 72 years; 13 (65%) were women. Median baseline NIHSS score was 13 (IQR 5-21). Six (30%) patients were comatose. Twelve patients (60%) received IVT. Median ΔNIHSS was -4 (IQR -11-+1). At follow-up, nine patients (45%) had mRS score 0-3. Seven (35%) died. eTICI 2b-3 was achieved in 13 patients (65%). Nine patients (45%) had periprocedural complications. No symptomatic intracranial hemorrhages (sICH) occurred.
Conclusions: EVT should be considered in selected patients with AIS with an isolated PCA occlusion, presenting with moderate-severe neurological deficits, as EVT was technically feasible in most of our patients and about half had good clinical outcome. In case of lower NIHSS score, a more conservative approach seems warranted, since periprocedural complications are not uncommon. Nonetheless, EVT seems reasonably safe considering the absence of sICH in our study.

Gepubliceerd: J Neurointerv Surg. 2023;15(4):363-9.
Impact factor: 4.9 ; Q1

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5. Successful reperfusion in relation to the number of passes: comparing outcomes of first pass expanded Treatment In Cerebral Ischemia (eTICI) 2B with multiple-pass eTICI 3
Bruggeman AAE, Kappelhof M, den Hartog SJ, Burke JF, Berkhemer OA, van Es A, van Zwam WH, Dippel DWJ, Coutinho JM, Marquering HA, Majoie C, Emmer BJ, MR CLEAN Registry investigators: Brouwers P, Bulut T.

Background: Higher expanded Treatment In Cerebral Ischemia (eTICI) reperfusion scores after endovascular treatment (EVT) are associated with better outcomes. However, the influence of the number of passes on this association is unclear. We aimed to compare outcomes of single-pass good reperfusion (eTICI 2B) with multiple-pass excellent/complete reperfusion (eTICI 2C/3) in daily clinical practice.
Methods: We compared outcomes of patients in the MR CLEAN Registry with good reperfusion (eTICI 2B) in a single pass to those with excellent/complete reperfusion (eTICI 2C/3) in multiple passes. Regression models were used to investigate the association of single-pass eTICI 2B versus multiple-pass eTICI 2C/3 reperfusion with 90-day functional outcome (modified Rankin Scale (mRS)), functional independence (mRS 0-2), per-procedural complications and safety outcomes.
Results: We included 699 patients: 178 patients with single-pass eTICI 2B, and 242 and 279 patients with eTICI 2C/3 after 2 and ≥3 passes, respectively. Patients with eTICI 2C/3 after 2 or ≥3 passes did not achieve significantly better functional outcomes compared with patients with single-pass eTICI 2B (adjusted common OR (acOR) 1.06, 95% CI 0.75 to 1.50 and acOR 0.88, 95% CI 0.74 to 1.05 for 90-day mRS, and adjusted OR (aOR) 1.24, 95% CI 0.78 to 1.97 and aOR 0.79, 95% CI 0.52 to 1.22 for functional independence).

Conclusions: Our results did not show better outcomes for patients who achieved eTICI 2C/3 in multiple, that is, two or more, passes when compared with patients with single-pass eTICI 2B. However, this concerns observational data. Further research is necessary to investigate the per-pass effect in relation to reperfusion and functional outcome.

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Impact factor: 4.9 ; Q1

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6. Development and Validation of a Postprocedural Model to Predict Outcome After Endovascular Treatment for Ischemic Stroke

Chalos V, Venema E, Mulder M, Roozenbeek B, Steyerberg EW, Wermer MJH, Lycklama À Nijeholt GJ, van der Worp HB, Goyal M, Campbell BCV, Muir KW, Guillemin F, Bracard S, White P, Dávalos A, Jovin TG, Hill MD, Mitchell PJ, Demchuk AM, Saver JL, van der Lugt A, Brown S, Dippel DWJ, Lingsma HF, MR CLEAN Registry Investigators: Brouwers P, Bulut T.

Importance: Outcome prediction after endovascular treatment (EVT) for ischemic stroke is important to patients, family members, and physicians.
Objective: To develop and validate a model based on preprocedural and postprocedural characteristics to predict functional outcome for individual patients after EVT.
Design, setting, and participants: A prediction model was developed using individual patient data from 7 randomized clinical trials, performed between December 2010 and December 2014. The model was developed within the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration and external validation in data from the Dutch Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry of patients treated in clinical practice between March 2014 and November 2017. Participants included patients from multiple centers throughout different countries in Europe, North America, East Asia, and Oceania (derivation cohort), and multiple centers in the Netherlands (validation cohort). Included were adult patients with a history of ischemic stroke from an intracranial large vessel occlusion in the anterior circulation who underwent EVT within 12 hours of symptom onset or last seen well. Data were last analyzed in July 2022.
Main outcome(s) and measure(s): A total of 19 variables were assessed by multivariable ordinal regression to predict functional outcome (modified Rankin Scale [mRS] score) 90 days after EVT. Variables were routinely available 1 day after EVT. Akaike information criterion (AIC) was used to optimize model fit vs model complexity. Probabilities for functional independence (mRS 0-2) and survival (mRS 0-5) were derived from the ordinal model. Model performance was expressed with discrimination (C statistic) and calibration.
Results: A total of 781 patients (median [IQR] age, 67 [57-76] years; 414 men [53%]) constituted the derivation cohort, and 3260 patients (median [IQR] age, 72 [61-80] years; 1684 men [52%]) composed the validation cohort. Nine variables were included in the model: age, baseline National Institutes of Health Stroke Scale (NIHSS) score, prestroke mRS score, history of diabetes, occlusion location, collateral score, reperfusion grade, NIHSS score at 24 hours, and symptomatic intracranial hemorrhage 24 hours after EVT. External validation in the MR CLEAN Registry showed excellent discriminative ability for functional independence (C statistic, 0.91; 95% CI, 0.90-0.92) and survival (0.89; 95% CI, 0.88-0.90). The proportion of functional independence in the MR CLEAN Registry was systematically higher than predicted by the model (41% vs 34%), whereas observed and predicted survival were similar (72% vs 75%). The model was updated and implemented for clinical use.
Conclusion and relevance: The prognostic tool MR PREDICTS@24H can be applied 1 day after EVT to accurately predict functional outcome for individual patients at 90 days and to provide reliable outcome expectations and personalize follow-up and rehabilitation plans. It will need further validation and updating for contemporary patients.

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Impact factor: 29.0 ; Q1

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7. Radiofrequency localization of nonpalpable breast cancer in a multicentre prospective cohort study: feasibility, clinical acceptability, and safety
Christenhusz A, den Dekker BM, van Dalen T, Jongen L, van der Schaaf MC, Alic L, Ten Haken B, Pijnappel RM, Dassen AE.

Purpose: In breast conserving surgery, accurate lesion localization is essential for obtaining adequate surgical margins. Preoperative wire localization (WL) and radioactive seed localization (RSL) are widely accepted methods to guide surgical excision of nonpalpable breast lesions but are limited by logistical challenges, migration issues, and legislative complexities. Radiofrequency identification (RFID) technology may offer a viable alternative. The purpose of this study was to evaluate the feasibility, clinical acceptability, and safety of RFID surgical guidance for localization of nonpalpable breast cancer.
Methods: In a prospective multicentre cohort study, the first 100 RFID localization procedures were included. The primary outcome was the percentage of clear resection margins and re-excision rate. Secondary outcomes included procedure details, user experience, learningcurve, and adverse events.
Results: Between April 2019 and May 2021, 100 women underwent RFID guided breast conserving surgery. Clear resection margins were obtained in 89 out of 96 included patients (92.7%), re-excision was indicated in three patients (3.1%). Radiologists reported difficulties with the placement of the RFID tag, partially related to the relatively large needle-applicator (12-gauge). This led to the premature termination of the study in the hospital using RSL as regular care. The radiologist experience was improved after a manufacturer modification of the needle-applicator. Surgical localization involved a low learning curve. Adverse events (n = 33) included dislocation of the marker during insertion (8%) and hematomas (9%). The majority of adverse events (85%) occurred using the first-generation needle-applicator.
Conclusion: RFID technology is a potential alternative for non-radioactive and non-wire localization of nonpalpable breast lesions.

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Impact factor: 3.8 ; Q2

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8. Primary central nervous system lymphoma
de Koning ME, Hof JJ, Jansen C, Doorduijn JK, Bromberg JEC, van der Meulen M.

Primary central nervous system lymphoma (PCNSL) is a rare type of non-Hodgkin lymphoma (NHL) manifesting in the brain, spinal cord, cerebrospinal fluid and/or eyes, in the absence of systemic manifestations. With an increasing incidence and a 30% 5-year overall survival if promptly treated, timely diagnosis and subsequent treatment is paramount. The typical MRI appearance for PCNSL is a solitary or multiple T2-hypointense, homogeneous gadolinium-enhancing lesion with restricted diffusion. Dexamethasone treatment might compromise and delay the diagnosis. Hallmark of treatment is induction with intravenous high-dose methotrexate consisting polychemotherapy followed by consolidation treatment. Consolidation treatment consists of either whole brain radiotherapy (WBRT) or autologous stem cell transplantation (ASCT). Given the (cognitive) side effects of WBRT, ASCT is increasingly being used as the first choice of treatment.

Gepubliceerd: J Neurol. 2023.
Impact factor: 6.0 ; Q1

9. Infarct Evolution in Patients with Anterior Circulation Large-Vessel Occlusion Randomized to IV Alteplase and Endovascular Treatment versus Endovascular Treatment Alone
Hoving JW, van Voorst H, Kappelhof M, Tolhuisen M, Treurniet KM, LeCouffe NE, Rinkel LA, Koopman MS, Cavalcante F, Konduri PR, van den Wijngaard IR, Ghariq E, Anton Meijer FJ, Coutinho JM, Marquering HA, Roos Y, Emmer BJ, Majoie C, MR CLEAN-NO IV Investigators: Bulut T.

Background and purpose: Infarct evolution after endovascular treatment varies widely among patients with stroke and may be affected by baseline characteristics and procedural outcomes. Moreover, IV alteplase and endovascular treatment may influence the relationship of these factors to infarct evolution. We aimed to assess whether the infarct evolution between baseline and follow-up imaging was different for patients who received IVT and EVT versus EVT alone.
Materials and methods: We included patients from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)-NO IV trial with baseline CTP and follow-up imaging. Follow-up infarct volume was segmented on 24-hour or 1-week follow-up DWI or NCCT. Infarct evolution was defined as the follow-up lesion volume: CTP core volume. Substantial infarct growth was defined as an increase in follow-up infarct volume of >10 mL. We assessed whether infarct evolution was different for patients with IV alteplase and endovascular treatment versus endovascular treatment alone and evaluated the association of baseline characteristics and procedural outcomes with infarct evolution using multivariable regression.
Results: From 228 patients with CTP results available, 145 patients had follow-up imaging and were included in our analysis. For patients with IV alteplase and endovascular treatment versus endovascular treatment alone, the baseline median CTP core volume was 17 (interquartile range = 4-35) mL versus 11 (interquartile range = 6-24) mL. The median follow-up infarct volume was 13 (interquartile range, 4-48) mL versus 17 (interquartile range = 4-50) mL. Collateral status and occlusion location were negatively associated with substantial infarct growth in patients with and without IV alteplase before endovascular treatment.
Conclusions: No statistically significant difference in infarct evolution was found in directly admitted patients who received IV alteplase and endovascular treatment within 4.5 hours of symptom onset versus patients who underwent endovascular treatment alone. Collateral status and occlusion location may be useful predictors of infarct evolution prognosis in patients eligible for IV alteplase who underwent endovascular treatment.

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Impact factor: 3.5 ; Q2

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10. Association between thrombus composition and stroke etiology in the MR CLEAN Registry biobank
Hund HM, Boodt N, Hansen D, Haffmans WA, Lycklama À Nijeholt GJ, Hofmeijer J, Dippel DWJ, van der Lugt A, van Es A, van Beusekom HMM, MR CLEAN Registry Investigators: Brouwers P, Bulut T.

Purpose: The composition of thrombi retrieved during endovascular thrombectomy (EVT) in acute ischemic stroke (AIS) due to large vessel occlusion (LVO) may differ depending on their origin. In this study, we investigated the association between thrombus composition and stroke etiology in a large population of patients from the Dutch MR CLEAN Registry treated with EVT in daily clinical practice.
Methods: The thrombi of 332 patients with AIS were histologically analyzed for red blood cells (RBC), fibrin/platelets (F/P), and white blood cells (leukocytes) using a machine learning algorithm. Stroke etiology was assessed using the Trial of Org 10,172 in acute stroke treatment (TOAST) classification.

Results: The thrombi of cardioembolic origin contained less RBC and more F/P than those of non-cardioembolic origin (25.8% vs 41.2% RBC [p = 0.003] and 67.1% vs 54.5% F/P [p = 0.004]). The likelihood of a non-cardioembolic source of stroke increased with increasing thrombus RBC content (OR 1.02; [95% CI 1.00-1.06] for each percent increase) and decreased with a higher F/P content (OR 1.02; [95% CI 1.00-1.06]). Thrombus composition in patients with a cardioembolic origin and undetermined origin was similar.
Conclusion: Thrombus composition is significantly associated with stroke etiology, with an increase in RBC and a decrease in F/P raising the odds for a non-cardioembolic cause. No difference between composition of cardioembolic thrombi and of undetermined origin was seen. This emphasizes the need for more extensive monitoring for arrhythmias and/or extended cardiac analysis in case of an undetermined origin.

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Impact factor: 2.8 ; Q3

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11. Clinical outcome of patients with mild pre-stroke morbidity following endovascular treatment: a HERMES substudy
McDonough RV, Ospel JM, Majoie C, Saver JL, White P, Dippel DWJ, Brown SB, Demchuk AM, Jovin TG, Mitchell PJ, Bracard S, Campbell BCV, Muir KW, Hill MD, Guillemin F, Goyal M, HERMES collaborators: Gerrits DG.

Background: Analyses of the effect of pre-stroke functional levels on the outcome of endovascular therapy (EVT) have focused on the course of patients with moderate to substantial pre-stroke disability. The effect of complete freedom from pre-existing disability (modified Rankin Scale (mRS) 0) versus predominantly mild pre-existing disability/symptoms (mRS 1-2) has not been well delineated.
Methods: The HERMES meta-analysis pooled data from seven randomized trials that tested the efficacy of EVT. We tested for a multiplicative interaction effect of pre-stroke mRS on the relationship between treatment and outcomes. Ordinal regression was used to assess the association between EVT and 90-day mRS (primary outcome) in the subgroup of patients with pre-stroke mRS 1-2. Multivariable regression modeling was then used to test the effect of mild pre-stroke disability/symptoms on the primary and secondary outcomes (delta-mRS, mRS 0-2/5-6) compared with patients with pre-stroke mRS 0.
Results: We included 1764 patients, of whom 199 (11.3%) had pre-stroke mRS 1-2. No interaction effect of pre-stroke mRS on the relationship between treatment and outcome was observed. Patients with pre-stroke mRS 1-2 had worse outcomes than those with pre-stroke mRS 0 (adjusted common OR (acOR) 0.53, 95% CI 0.40 to 0.70). Nonetheless, a significant benefit of EVT was observed within the mRS 1-2 subgroup (cOR 2.08, 95% CI 1.22 to 3.55).
Conclusions: Patients asymptomatic/without disability prior to onset have better outcomes following EVT than patients with mild disability/symptoms. Patients with pre-stroke mRS 1-2, however, more often achieve good outcomes with EVT compared with conservative management. These findings indicate that mild pre-existing disability/symptoms influence patient prognosis after EVT but do not diminish the EVT treatment effect.

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Impact factor: 4.9 ; Q1

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12. Endovascular treatment versus no endovascular treatment after 6-24 h in patients with ischaemic stroke and collateral flow on CT angiography (MR CLEAN-LATE) in the Netherlands: a multicentre, open-label, blinded-endpoint, randomised, controlled, phase 3 trial

Olthuis SGH, Pirson FAV, Pinckaers FME, Hinsenveld WH, Nieboer D, Ceulemans A, Knapen R, Robbe MMQ, Berkhemer OA, van Walderveen MAA, Lycklama À Nijeholt GJ, Uyttenboogaart M, Schonewille WJ, van der Sluijs PM, Wolff L, van Voorst H, Postma AA, Roosendaal SD, van der Hoorn A, Emmer BJ, Krietemeijer MGM, van Doormaal PJ, Roozenbeek B, Goldhoorn RB, Staals J, de Ridder IR, van der Leij C, Coutinho JM, van der Worp HB, Lo RTH, Bokkers RPH, van Dijk EI, Boogaarts HD, Wermer MJH, van Es A, van Tuijl JH, Kortman HGJ, Gons RAR, Yo LSF, Vos JA, de Laat KF, van Dijk LC, van den Wijngaard IR, Hofmeijer J, Martens JM, Brouwers P, Bulut T, Remmers MJM, de Jong T, den Hertog HM, van Hasselt B, Rozeman AD, Elgersma OEH, van der Veen B, Sudiono DR, Lingsma HF, Roos Y, Majoie C, van der Lugt A, Dippel DWJ, van Zwam WH, van Oostenbrugge RJ.

Background: Endovascular treatment for anterior circulation ischaemic stroke is effective and safe within a 6 h window. MR CLEAN-LATE aimed to assess efficacy and safety of endovascular treatment for patients treated in the late window (6-24 h from symptom onset or last seen well) selected on the basis of the presence of collateral flow on CT angiography (CTA).
Methods: MR CLEAN-LATE was a multicentre, open-label, blinded-endpoint, randomised, controlled, phase 3 trial done in 18 stroke intervention centres in the Netherlands. Patients aged 18 years or older with ischaemic stroke, presenting in the late window with an anterior circulation large-vessel occlusion and collateral flow on CTA, and a neurological deficit score of at least 2 on the National Institutes of Health Stroke Scale were included. Patients who were eligible for late-window endovascular treatment were treated according to national guidelines (based on clinical and perfusion imaging criteria derived from the DAWN and DEFUSE-3 trials) and excluded from MR CLEAN-LATE enrolment. Patients were randomly assigned (1:1) to receive endovascular treatment or no endovascular treatment (control), in addition to best medical treatment. Randomisation was web based, with block sizes ranging from eight to 20, and stratified by centre. The primary outcome was the modified Rankin Scale (mRS) score at 90 days after randomisation. Safety outcomes included all-cause mortality at 90 days after randomisation and symptomatic intracranial haemorrhage. All randomly assigned patients who provided deferred consent or died before consent could be obtained comprised the modified intention-to-treat population, in which the primary and safety outcomes were assessed. Analyses were adjusted for predefined confounders. Treatment effect was estimated with ordinal logistic regression and reported as an adjusted common odds ratio (OR) with a 95% CI. This trial was registered with the ISRCTN, ISRCTN19922220.
Findings: Between Feb 2, 2018, and Jan 27, 2022, 535 patients were randomly assigned, and 502 (94%) patients provided deferred consent or died before consent was obtained (255 in the endovascular treatment group and 247 in the control group; 261 [52%] females). The median mRS score at 90 days was lower in the endovascular treatment group than in the control group (3 [IQR 2-5] vs 4 [2-6]), and we observed a shift towards better outcomes on the mRS for the endovascular treatment group (adjusted common OR 1·67 [95% CI 1·20-2·32]). All-cause mortality did not differ significantly between groups (62 [24%] of 255 patients vs 74 [30%] of 247 patients; adjusted OR 0·72 [95% CI 0·44-1·18]). Symptomatic intracranial haemorrhage occurred more often in the endovascular treatment group than in the control group (17 [7%] vs four [2%]; adjusted OR 4·59 [95% CI 1·49-14·10]).
Interpretation: In this study, endovascular treatment was efficacious and safe for patients with ischaemic stroke caused by an anterior circulation large-vessel occlusion who presented 6-24 h from onset or last seen well, and who were selected on the basis of the presence of collateral flow on CTA. Selection of patients for endovascular treatment in the late window could be primarily based on the presence of collateral flow.
Funding: Collaboration for New Treatments of Acute Stroke consortium, Dutch Heart Foundation, Stryker, Medtronic, Cerenovus, Top Sector Life Sciences & Health, and the Netherlands Brain Foundation.

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Impact factor: 168.9 ; Q1

13. Imaging breast malignancies with the Twente Photoacoustic Mammoscope 2
Schoustra SM, De Santi B, Op 't Root T, Klazen CAH, van der Schaaf M, Veltman J, Steenbergen W, Manohar S.

Clinical measurements on breast cancer patients were performed with a three-dimensional tomographic photoacoustic prototype imager (PAM 2). Patients with a suspicious lesion, visiting the center for breast care of a local hospital, were included in the study. The acquired photoacoustic images were compared to conventional clinical images. Of 30 scanned patients, 19 were diagnosed with one or more malignancies, of which a subset of four patients was selected for detailed analysis. Reconstructed images were processed to enhance image quality and the visibility of blood vessels. Processed photoacoustic images were compared to contrast-enhanced magnetic resonance images where available, which aided in localizing the expected tumoral region. In two cases, spotty high-intensity photoacoustic signals could be seen in the tumoral region, attributable to the tumor. One of these cases also displayed a relatively high image entropy at the tumor site, likely related to the chaotic vascular networks associated with malignancies. For the other two cases, it was not possible to identify features indicative of malignancy, because of limitations in the illumination scheme and difficulties in locating the region of interest in the photoacoustic image.

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Impact factor: 3.7 ; Q2

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14. Collateral status and recanalization after endovascular treatment for acute ischemic stroke
Uniken Venema SM, Dankbaar JW, Wolff L, van Es A, Sprengers M, van der Lugt A, Dippel DWJ, van der Worp HB, MR CLEAN Registry investigators: Brouwers P, Bulut T.

Background: Successful recanalization and good collateral status are associated with good clinical outcomes after endovascular treatment (EVT) for acute ischemic stroke, but the relationships among them are unclear.
Objective: To assess if collateral status is associated with recanalization after EVT and if collateral status modifies the association between successful recanalization and functional outcome.
Methods: We retrospectively analyzed data from the MR CLEAN Registry, a multicenter prospective cohort study of patients with a proximal anterior occlusion who underwent EVT in the Netherlands. We determined collateral status with a previously validated four-point visual grading scale and defined successful recanalization as an extended Thrombolysis in Cerebral Infarction score ≥2B. Functional outcome was determined using the modified Rankin Scale score at 90 days. We assessed, with multivariable logistic regression models, the associations between (1) collateral status and successful recanalization, (2) successful recanalization and functional outcome, (3) collateral status and functional outcome. An interaction of collateral status and successful recanalization was assessed. Subgroup analyses were performed for patients treated with intravenous thrombolysis.
Results: We included 2717 patients, of whom 1898 (70%) had successful recanalization. There was no relationship between collateral status and successful recanalization (adjusted common OR (95% CI) of grades 1, 2, and 3 vs 0: 1.19 (0.82 to 1.72), 1.20 (0.83 to 1.75), and 1.10 (0.74 to 1.63), respectively). Successful recanalization (acOR (95% CI): 2.15 (1.84 to 2.52)) and better collateral grades (acOR (95% CI) of grades 1, 2, and 3 vs 0: 2.12 (1.47 to 3.05), 3.46 (2.43 to 4.92), and 4.16 (2.89 to 5.99), respectively) were both associated with a shift towards better functional outcome, without an interaction between collateral status and successful recanalization. Results were similar for the subgroup of thrombolysed patients.

Conclusions: Collateral status is not associated with the probability of successful recanalization after EVT and does not modify the association between successful recanalization and functional outcome.

Gepubliceerd: J Neurointerv Surg. 2023;15(6):531-8.
Impact factor: 4.9 ; Q1

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15. Hemorrhage rates in patients with acute ischemic stroke treated with intravenous alteplase and thrombectomy versus thrombectomy alone
van Kranendonk KR, Kappelhof M, Bruggeman AAE, Rinkel LA, Treurniet KM, LeCouffe N, Emmer BJ, Coutinho JM, Wolff L, van Zwam WH, van Oostenbrugge RJ, van der Lugt A, Dippel DWJ, Roos Y, Marquering HA, Majoie C, MR CLEAN-NO IV Investigators: Brouwers P, Bulut T.

Background: Intravenous alteplase treatment (IVT) for acute ischemic stroke carries a risk of intracranial hemorrhage (ICH). However, reperfusion of an occluded vessel itself may contribute to the risk of ICH. We determined whether IVT and reperfusion are associated with ICH or its volume in the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN)-NO IV trial.
Methods: The MR CLEAN-NO IV trial randomized patients with acute ischemic stroke due to large vessel occlusion to receive either IVT followed by endovascular treatment (EVT) or EVT alone. ICH was classified according to the Heidelberg bleeding classification on follow-up MRI or CT approximately 8 hours-7 days after stroke. Hemorrhage volume was measured with ITK-snap. Successful reperfusion was defined as extended Thrombolysis In Cerebral Infarction (eTICI) score of 2b-3. Multinomial and binary adjusted logistic regression were used to determine the association of IVT and reperfusion with ICH subtypes.
Results: Of 539 included patients, 173 (32%) developed ICH and 30 suffered from symptomatic ICH (sICH) (6%). Of the patients with ICH, 102 had hemorrhagic infarction, 47 had parenchymal hematoma, 44 had SAH, and six had other ICH. Reperfusion was associated with a decreased risk of SAH, and IVT was not associated with SAH (eTICI 2b-3: adjusted OR 0.45, 95% CI 0.21 to 0.97; EVT without IVT: OR 1.6, 95% CI 0.91 to 2.8). Reperfusion status and IVT were not associated with overall ICH, hemorrhage volume, and sICH (sICH: EVT without IVT, OR 0.96, 95% CI 0.41 to 2.25; eTICI 2b-3, OR 0.49, 95% CI 0.23 to 1.05).
Conclusion: Neither IVT administration before EVT nor successful reperfusion after EVT were associated with ICH, hemorrhage volume, and sICH. SAH occurred more often in patients for whom successful reperfusion was not achieved.

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Impact factor: 4.9 ; Q1

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16. Prognostic Value of Thrombus Volume and Interaction With First-Line Endovascular Treatment Device Choice
van Voorst H, Bruggeman AAE, Andriessen J, Hoving JW, Konduri PR, Yang W, Kappelhof M, Arrarte Terreros N, Roos Y, van Zwam WH, van der Lugt A, van der Hoorn A, Boiten J, Roosendaal S, Jenniskens S, Caan MWA, Marquering HA, Emmer BJ, Majoie C, MR CLEAN Registry investigators: Brouwers P, Bulut T.

Background: A larger thrombus in patients with acute ischemic stroke might result in more complex endovascular treatment procedures, resulting in poorer patient outcomes. Current evidence on thrombus volume and length related to procedural and functional outcomes remains contradicting. This study aimed to assess the prognostic value of thrombus volume and thrombus length and

whether this relationship differs between first-line stent retrievers and aspiration devices for endovascular treatment.
Methods: In this multicenter retrospective cohort study, 670 of 3279 patients from the MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) for endovascularly treated large vessel occlusions were included. Thrombus volume (0.1 mL) and length (0.1 mm) based on manual segmentations and measurements were related to reperfusion grade (expanded Treatment in Cerebral Infarction score) after endovascular treatment, the number of retrieval attempts, symptomatic intracranial hemorrhage, and a shift for functional outcome at 90 days measured with the reverted ordinal modified Rankin Scale (odds ratio >1 implies a favorable outcome). Univariable and multivariable linear and logistic regression were used to report common odds ratios (cORs)/adjusted cOR and regression coefficients (B/aB) with 95% CIs. Furthermore, a multiplicative interaction term was used to analyze the relationship between first-line device choice, stent retrievers versus aspiration device, thrombus volume, and outcomes.
Results: Thrombus volume was associated with functional outcome (adjusted cOR, 0.83 [95% CI, 0.71-0.97]) and number of retrieval attempts (aB, 0.16 [95% CI, 0.16-0.28]) but not with the other outcome measures. Thrombus length was only associated with functional independence (adjusted cOR, 0.45 [95% CI, 0.24-0.85]). Patients with more voluminous thrombi had worse functional outcomes if endovascular treatment was based on first-line stent retrievers (interaction cOR, 0.67 [95% CI, 0.50-0.89]; *P*=0.005; adjusted cOR, 0.74 [95% CI, 0.55-1.0]; *P*=0.04).
Conclusions: In this study, patients with a more voluminous thrombus required more endovascular thrombus retrieval attempts and had a worse functional outcome. Patients with a lengthier thrombus were less likely to achieve functional independence at 90 days. For more voluminous thrombi, first-line stent retrieval compared with first-line aspiration might be associated with worse functional outcome.

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Impact factor: 8.4 ; Q1

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17. Costs and health effects of CT perfusion-based selection for endovascular thrombectomy within 6 hours of stroke onset: a model-based health economic evaluation
van Voorst H, Hoving JW, Koopman MS, Daems JD, Peerlings D, Buskens E, Lingsma H, Marquering HA, de Jong H, Berkhemer OA, van Zwam WH, van Walderveen MAA, van den Wijngaard IR, Dippel DWJ, Yoo AJ, Campbell B, Kunz WG, Majoie CB, Emmer BJ, MR CLEAN Registry investigators: Brouwers P, Bulut T.

Background: Although CT perfusion (CTP) is often incorporated in acute stroke workflows, it remains largely unclear what the associated costs and health implications are in the long run of CTP-based patient selection for endovascular treatment (EVT) in patients presenting within 6 hours after symptom onset with a large vessel occlusion.
Methods: Patients with a large vessel occlusion were included from a Dutch nationwide cohort (n=703) if CTP imaging was performed before EVT within 6 hours after stroke onset. Simulated cost and health effects during 5 and 10 years follow-up were compared between CTP based patient selection for EVT and providing EVT to all patients. Outcome measures were the net monetary benefit at a willingness-to-pay of €80 000 per quality-adjusted life year, incremental cost-effectiveness ratio), difference in costs from a healthcare payer perspective (ΔCosts) and quality-adjusted life years (ΔQALY) per 1000 patients for 1000 model iterations as outcomes.
Results: Compared with treating all patients, CTP-based selection for EVT at the optimised ischaemic core volume (ICV≥110 mL) or core-penumbra mismatch ratio (MMR≤1.4) thresholds resulted in losses of health (median ΔQALYs for ICV≥110 mL: -3.3 (IQR: -5.9 to -1.1), for MMR≤1.4: 0.0 (IQR: -1.3 to 0.0)) with median ΔCosts for ICV≥110 mL of -€348 966 (IQR: -€712 406 to -€51 158) and for MMR≤1.4 of €266 513 (IQR: €229 403 to €380 110)) per 1000 patients. Sensitivity analyses did not yield any

scenarios for CTP-based selection of patients for EVT that were cost-effective for improving health, including patients aged ≥80 years CONCLUSION: In EVT-eligible patients presenting within 6 hours after symptom onset, excluding patients based on CTP parameters was not cost-effective and could potentially harm patients.

Gepubliceerd: J Neurol Neurosurg Psychiatry. 2023.
Impact factor: 11.1 ; Q1

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18. Baseline and early digital [18 F]FDG PET/CT and multiparametric MRI contain promising features to predict response to neoadjuvant therapy in locally advanced rectal cancer patients: a pilot study
Vuijk FA, Feshtali Shahbazi S, Noortman WA, van Velden FHP, Dibbets-Schneider P, Marinelli A, Neijenhuis PA, Schmitz R, Ghariq E, Velema LA, Peters FP, Smit F, Peeters K, Temmink SJD, Crobach S, Putter H, Vahrmeijer AL, Hilling DE, de Geus-Oei LF.

Objective: In this pilot study, we investigated the feasibility of response prediction using digital [18 F]FDG PET/computed tomography (CT) and multiparametric MRI before, during, and after neoadjuvant chemoradiation therapy in locally advanced rectal cancer (LARC) patients and aimed to select the most promising imaging modalities and timepoints for further investigation in a larger trial.
Methods: Rectal cancer patients scheduled to undergo neoadjuvant chemoradiation therapy were prospectively included in this trial, and underwent multiparametric MRI and [18 F]FDG PET/CT before, 2 weeks into, and 6-8 weeks after chemoradiation therapy. Two groups were created based on pathological tumor regression grade, that is, good responders (TRG1-2) and poor responders (TRG3-5). Using binary logistic regression analysis with a cutoff value of $P \leq 0.2$, promising predictive features for response were selected.
Results: Nineteen patients were included. Of these, 5 were good responders, and 14 were poor responders. Patient characteristics of these groups were similar at baseline. Fifty-seven features were extracted, of which 13 were found to be promising predictors of response. Baseline [T2: volume, diffusion-weighted imaging (DWI): apparent diffusion coefficient (ADC) mean, DWI: difference entropy], early response (T2: volume change, DWI: ADC mean change) and end-of-treatment presurgical evaluation MRI (T2: gray level nonuniformity, DWI: inverse difference normalized, DWI: gray level nonuniformity normalized), as well as baseline (metabolic tumor volume, total lesion glycolysis) and early response PET/CT (Δ maximum standardized uptake value, Δ peak standardized uptake value corrected for lean body mass), were promising features.
Conclusion: Both multiparametric MRI and [18 F]FDG PET/CT contain promising imaging features to predict response to neoadjuvant chemoradiotherapy in LARC patients. A future larger trial should investigate baseline, early response, and end-of-treatment presurgical evaluation MRI and baseline and early response PET/CT.

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Impact factor: 1.5 ; Q4

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19. Evaluation of National Surgical Practice for Lateral Lymph Nodes in Rectal Cancer in an Untrained Setting
Sluckin TC, Hazen SJA, Horsthuis K, Beets-Tan RGH, Aalbers AGJ, Beets GL, Boerma EG, Borstlap J, van Breest Smallenburg V, Burger JWA, Crolla R, Daniëls-Gooszen AW, Davids PHP, Dunker MS, Fabry HFJ, Furnée EJB, van Gils RAH, de Haas RJ, Hoogendoorn S, van Koeverden S, de Korte FI, Oosterling SJ, Peeters K, Posma LAE, Pultrum BB, Rothbarth J, Rutten HJT, Schasfoort RA, Schreurs WH, Simons PCG, Smits AB, Talsma AK, The GYM, van Tilborg F, Tuynman JB, Vanhooymissen IJS, van de Ven AWH,

Verdaasdonk EGG, Vermaas M, Vliegen RFA, Vogelaar FJ, de Vries M, Vroemen JC, van Vugt ST, Westerterp M, van Westreenen HL, de Wilt JHW, van der Zaag ES, Zimmerman DDE, Marijnen CAM, Tanis PJ, Kusters M, Dutch Snapshot Research Group.

Background: Involved lateral lymph nodes (LLNs) have been associated with increased local recurrence (LR) and ipsi-lateral LR (LLR) rates. However, consensus regarding the indication and type of surgical treatment for suspicious LLNs is lacking. This study evaluated the surgical treatment of LLNs in an untrained setting at a national level.
Methods: Patients who underwent additional LLN surgery were selected from a national cross-sectional cohort study regarding patients undergoing rectal cancer surgery in 69 Dutch hospitals in 2016. LLN surgery consisted of either 'node-picking' (the removal of an individual LLN) or 'partial regional node dissection' (PRND; an incomplete resection of the LLN area). For all patients with primarily enlarged (≥7 mm) LLNs, those undergoing rectal surgery with an additional LLN procedure were compared to those undergoing only rectal resection.
Results: Out of 3057 patients, 64 underwent additional LLN surgery, with 4-year LR and LLR rates of 26% and 15%, respectively. Forty-eight patients (75%) had enlarged LLNs, with corresponding recurrence rates of 26% and 19%, respectively. Node-picking (n = 40) resulted in a 20% 4-year LLR, and a 14% LLR after PRND (n = 8; p = 0.677). Multivariable analysis of 158 patients with enlarged LLNs undergoing additional LLN surgery (n = 48) or rectal resection alone (n = 110) showed no significant association of LLN surgery with 4-year LR or LLR, but suggested higher recurrence risks after LLN surgery (LR: hazard ratio [HR] 1.5, 95% confidence interval [CI] 0.7-3.2, p = 0.264; LLR: HR 1.9, 95% CI 0.2-2.5, p = 0.874).
Conclusion: Evaluation of Dutch practice in 2016 revealed that approximately one-third of patients with primarily enlarged LLNs underwent surgical treatment, mostly consisting of node-picking. Recurrence rates were not significantly affected by LLN surgery, but did suggest worse outcomes. Outcomes of LLN surgery after adequate training requires further research.

Gepubliceerd: Ann Surg Oncol. 2023;30(9):5472-85.
Impact factor: 3.7 ; Q1

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20. An updated evaluation of the implementation of the sigmoid take-off landmark 1 year after the official introduction in the Netherlands

Hazen SJA, Sluckin TC, Horsthuis K, Lambregts DMJ, Beets-Tan RGH, Tanis PJ, Kusters M, Dutch Sigmoid Take-off Research Group

Purpose: The definition of rectal cancer based on the sigmoid take-off (STO) was incorporated into the Dutch guideline in 2019, and became mandatory in the national audit from December 2020. This study aimed to evaluate the use of the STO in clinical practice and the added value of online training, stratified for the period before (group A, historical cohort) and after (group B, current cohort) incorporation into the national audit.
Methods: Participants, including radiologists, surgeons, surgical and radiological residents, interns, PhD students, and physician assistants, were asked to complete an online training program, consisting of questionnaires, 20 MRI cases, and a training document. Outcomes were agreement with the expert reference, inter-rater variability, and accuracy before and after the training.
Results: Group A consisted of 86 participants and group B consisted of 114 participants. Familiarity with the STO was higher in group B (76% vs 88%, p = 0.027). Its use in multidisciplinary meetings was not significantly higher (50% vs 67%, p = 0.237). Agreement with the expert reference was similar for both groups before (79% vs 80%, p = 0.423) and after the training (87% vs 87%, p = 0.848). Training resulted in significant improvement for both groups in classifying tumors located around the STO (group A, 69-79%; group B, 67-79%, p < 0.001).

Conclusions: The results of this study show that after the inclusion of the STO in the mandatory Dutch national audit, the STO was consequently used in only 67% of the represented hospitals. Online training has the potential to improve implementation and unambiguous assessment.

Gepubliceerd: Tech Coloproctol 2023;27(12):1243-1250.
Impact factor: 2.7 ; Q1

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21. Dynamic phase-locking states and personality in sub-acute mild traumatic brain injury: An exploratory study
van der Horn HJ, de Koning ME, Visser K, Kok MGJ, Spikman JM, Scheenen ME, Renken RJ, Calhoun VD, Vergara VM, Cabral J, Mayer AR, van der Naalt J.

Research has shown that maladaptive personality characteristics, such as Neuroticism, are associated with poor outcome after mild traumatic brain injury (mTBI). The current exploratory study investigated the neural underpinnings of this process using dynamic functional network connectivity (dFNC) analyses of resting-state (rs) fMRI, and diffusion MRI (dMRI). Twenty-seven mTBI patients and 21 healthy controls (HC) were included. After measuring the Big Five personality dimensions, principal component analysis (PCA) was used to obtain a superordinate factor representing emotional instability, consisting of high Neuroticism, moderate Openness, and low Extraversion, Agreeableness, and Conscientiousness. Persistent symptoms were measured using the head injury symptom checklist at six months post-injury; symptom severity (i.e., sum of all items) was used for further analyses. For patients, brain MRI was performed in the sub-acute phase (~1 month) post-injury. Following parcellation of rs-fMRI using independent component analysis, leading eigenvector dynamic analysis (LEiDA) was performed to compute dynamic phase-locking brain states. Main patterns of brain diffusion were computed using tract-based spatial statistics followed by PCA. No differences in phase-locking state measures were found between patients and HC. Regarding dMRI, a trend significant decrease in fractional anisotropy was found in patients relative to HC, particularly in the fornix, genu of the corpus callosum, anterior and posterior corona radiata. Visiting one specific phase-locking state was associated with lower symptom severity after mTBI. This state was characterized by two clearly delineated communities (each community consisting of areas with synchronized phases): one representing an executive/saliency system, with a strong contribution of the insulae and basal ganglia; the other representing the canonical default mode network. In patients who scored high on emotional instability, this relationship was even more pronounced. Dynamic phase-locking states were not related to findings on dMRI. Altogether, our results provide preliminary evidence for the coupling between personality and dFNC in the development of long-term symptoms after mTBI.

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Impact factor: 3.7 ; Q2

Totale impact factor: 218.0
Gemiddelde impact factor: 10.4

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 1
Totale impact factor: 6.0
Gemiddelde impact factor: 6.0

Radiotherapie

1. Interpretable deep learning model to predict the molecular classification of endometrial cancer from haematoxylin and eosin-stained whole-slide images: a combined analysis of the PORTEC randomised trials and clinical cohorts

Fremond S, Andani S, Barkey Wolf J, Dijkstra J, Melsbach S, Jobsen JJ, Brinkhuis M, Roothaan S, Jurgenliemk-Schulz I, Lutgens L, Nout RA, van der Steen-Banasik EM, de Boer SM, Powell ME, Singh N, Mileshkin LR, Mackay HJ, Leary A, Nijman HW, Smit V, Creutzberg CL, Horeweg N, Koelzer VH, Bosse T.

Background: Endometrial cancer can be molecularly classified into POLE^{mut}, mismatch repair deficient (MMRd), p53 abnormal (p53abn), and no specific molecular profile (NSMP) subgroups. We aimed to develop an interpretable deep learning pipeline for whole-slide-image-based prediction of the four molecular classes in endometrial cancer (im4MEC), to identify morpho-molecular correlates, and to refine prognostication.
Methods: This combined analysis included diagnostic haematoxylin and eosin-stained slides and molecular and clinicopathological data from 2028 patients with intermediate-to-high-risk endometrial cancer from the PORTEC-1 (n=466), PORTEC-2 (n=375), and PORTEC-3 (n=393) randomised trials and the TransPORTEC pilot study (n=110), the Medisch Spectrum Twente cohort (n=242), a case series of patients with POLE^{mut} endometrial cancer in the Leiden Endometrial Cancer Repository (n=47), and The Cancer Genome Atlas-Uterine Corpus Endometrial Carcinoma cohort (n=395). PORTEC-3 was held out as an independent test set and a four-fold cross validation was performed. Performance was measured with the macro and class-wise area under the receiver operating characteristic curve (AUROC). Whole-slide images were segmented into tiles of 360 µm resized to 224 × 224 pixels. im4MEC was trained to learn tile-level morphological features with self-supervised learning and to molecularly classify whole-slide images with an attention mechanism. The top 20 tiles with the highest attention scores were reviewed to identify morpho-molecular correlates. Predictions of a nuclear classification deep learning model serve to derive interpretable morphological features. We analysed 5-year recurrence-free survival and explored prognostic refinement by molecular class using the Kaplan-Meier method.
Findings: im4MEC attained macro-average AUROCs of 0·874 (95% CI 0·856-0·893) on four-fold cross-validation and 0·876 on the independent test set. The class-wise AUROCs were 0·849 for POLE^{mut} (n=51), 0·844 for MMRd (n=134), 0·883 for NSMP (n=120), and 0·928 for p53abn (n=88). POLE^{mut} and MMRd tiles had a high density of lymphocytes, p53abn tiles had strong nuclear atypia, and the morphology of POLE^{mut} and MMRd endometrial cancer overlapped. im4MEC highlighted a low tumour-to-stroma ratio as a potentially novel characteristic feature of the NSMP class. 5-year recurrence-free survival was significantly different between im4MEC predicted molecular classes in PORTEC-3 (log-rank p<0·0001). The ten patients with aggressive p53abn endometrial cancer that was predicted as MMRd showed inflammatory morphology and appeared to have a better prognosis than patients with correctly predicted p53abn endometrial cancer (p=0·30). The four patients with NSMP endometrial cancer that was predicted as p53abn showed higher nuclear atypia and appeared to have a worse prognosis than patients with correctly predicted NSMP (p=0·13). Patients with MMRd endometrial cancer predicted as POLE^{mut} had an excellent prognosis, as do those with true POLE^{mut} endometrial cancer.
Interpretation: We present the first interpretable deep learning model, im4MEC, for haematoxylin and eosin-based prediction of molecular endometrial cancer classification. im4MEC robustly identified morpho-molecular correlates and could enable further prognostic refinement of patients with endometrial cancer.
Funding: The Hanarth Foundation, the Promedica Foundation, and the Swiss Federal Institutes of Technology.

Gepubliceerd: Lancet Digit Health. 2023;5(2):e71-e82.

Impact factor: 30.8 ; Q1

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2. Molecular Classification Predicts Response to Radiotherapy in the Randomized PORTEC-1 and PORTEC-2 Trials for Early-Stage Endometrioid Endometrial Cancer
Horeweg N, Nout RA, Jurgenliemk-Schulz IM, Lutgens L, Jobsen JJ, Haverkort MAD, Mens JWM, Slot A, Wortman BG, de Boer SM, Stelloo E, Verhoeven-Adema KW, Putter H, Smit V, Bosse T, Creutzberg CL, Group PS.

Purpose: The molecular classification of endometrial cancer (EC) has proven to have prognostic value and is predictive of response to adjuvant chemotherapy. Here, we investigate its predictive value for response to external beam radiotherapy (EBRT) and vaginal brachytherapy (VBT) in early-stage endometrioid EC (EEC).
Methods: Data of the randomized PORTEC-1 trial (n = 714) comparing pelvic EBRT with no adjuvant therapy in early-stage intermediate-risk EC and the PORTEC-2 trial (n = 427) comparing VBT with EBRT in early-stage high-intermediate-risk EC were used. Locoregional (including vaginal and pelvic) recurrence-free survival was compared between treatment groups across the four molecular classes using Kaplan-Meier's methodology and log-rank tests.
Results: A total of 880 molecularly classified ECs, 484 from PORTEC-1 and 396 from PORTEC-2, were included. The majority were FIGO-2009 stage I EEC (97.2%). The median follow-up was 11.3 years. No locoregional recurrences were observed in EC with a pathogenic mutation of DNA polymerase-ε (*POLE*mut EC). In mismatch repair-deficient (MMRd) EC, locoregional recurrence-free survival was similar after EBRT (94.2%), VBT (94.2%), and no adjuvant therapy (90.3%; *P* = .74). In EC with a p53 abnormality (p53abn EC), EBRT (96.9%) had a substantial benefit over VBT (64.3%) and no adjuvant therapy (72.2%; *P* = .048). In EC with no specific molecular profile (NSMP EC), both EBRT (98.3%) and VBT (96.2%) yielded better locoregional control than no adjuvant therapy (87.7%; *P* < .0001).
Conclusion: The molecular classification of EC predicts response to radiotherapy in stage I EEC and may guide adjuvant treatment decisions. Omitting radiotherapy seems to be safe in *POLE*mut EC. The benefit of radiotherapy seems to be limited in MMRd EC. EBRT yields a significantly better locoregional recurrence-free survival than VBT or no adjuvant therapy in p53abn EC. VBT is the treatment of choice for NSMP EC as it is as effective as EBRT and significantly better than no adjuvant therapy for locoregional tumor control.
Trial registration: ClinicalTrials.gov NCT00376844.

Gepubliceerd: J Clin Oncol. 2023;41(27):4369-80.
Impact factor: 45.4 ; Q1

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3. Clinical Behavior and Molecular Landscape of Stage I p53-Abnormal Low-Grade Endometrioid Endometrial Carcinomas
Jamieson A, Vermij L, Kramer CJH, Jobsen JJ, Jurgemlienk-Schulz I, Lutgens L, Mens JW, Haverkort MAD, Slot A, Nout RA, Oosting J, Carlson J, Howitt BE, Ip PPC, Lax SF, McCluggage WG, Singh N, McAlpine JN, Creutzberg CL, Horeweg N, Gilks CB, Bosse T.

Purpose: The clinical significance of the p53-abnormal (p53abn) molecular subtype in stage I low-grade endometrioid endometrial carcinoma (EEC) is debated. We aimed to review pathologic and molecular characteristics, and outcomes of stage I low-grade p53abn EEC in a large international cohort.
Experimental design: Previously diagnosed stage I p53abn EC (POLE-wild-type, mismatch repair-proficient) low-grade EEC from Canadian retrospective cohorts and PORTEC-1&2 trials were included. Pathology review was performed by six expert gynecologic pathologists blinded to p53 status. IHC

profiling, next-generation sequencing, and shallow whole-genome sequencing was performed. Kaplan-Meier method was used for survival analysis.
Results: We identified 55 stage I p53abn low-grade EEC among 3,387 cases (2.5%). On pathology review, 17 cases (31%) were not diagnosed as low-grade EEC by any pathologists, whereas 26 cases (47%) were diagnosed as low-grade EEC by at least three pathologists. The IHC and molecular profile of the latter cases were consistent with low-grade EEC morphology (ER/PR positivity, patchy p16 expression, PIK3CA and PTEN mutations) but they also showed features of p53abn EC (TP53 mutations, many copy-number alterations). These cases had a clinically relevant risk of disease recurrence (5-year recurrence-free survival 77%), with pelvic and/or distant recurrences observed in 12% of the patients.
Conclusions: A subset of p53abn EC is morphologically low-grade EEC and exhibit genomic instability. Even for stage I disease, p53abn low-grade EEC are at substantial risk of disease recurrence. These findings highlight the clinical relevance of universal p53-testing, even in low-grade EEC, to identify women at increased risk of recurrence.

Gepubliceerd: Clin Cancer Res. 2023;29(23):4949-57.
Impact factor: 11.5 ; Q1

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4. 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. 2023;37:103292.
Impact factor: 4.2 ; Q2

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5. QPOLE: A Quick, Simple, and Cheap Alternative for POLE Sequencing in Endometrial Cancer by Multiplex Genotyping Quantitative Polymerase Chain Reaction
Van den Heerik A, Ter Haar NT, Vermij L, Jobsen JJ, Brinkhuis M, Roothaan SM, Leon-Castillo A, Ortoft G, Hogdall E, Hogdall C, Van Wezel T, Lutgens L, Haverkort MAD, Khattra J, McAlpine JN, Creutzberg CL, Smit V, Gilks CB, Horeweg N, Bosse T.

Purpose: Detection of 11 pathogenic variants in the *POLE* gene in endometrial cancer (EC) is critically important to identify women with a good prognosis and reduce overtreatment.
Currently, *POLE* status is determined by DNA sequencing, which can be expensive, relatively time-consuming, and unavailable in hospitals without specialized equipment and personnel. This may hamper the implementation of *POLE*-testing in clinical practice. To overcome this, we developed and validated a rapid, low-cost *POLE* hotspot test by a quantitative polymerase chain reaction (qPCR) assay, *QPOLE*.
Materials and methods: Primer and fluorescence-labeled 5'-nuclease probe sequences of the 11 established pathogenic *POLE* mutations were designed. Three assays, *QPOLE*-frequent for the most common mutations and *QPOLE*-rare-1 and QPOLE-rare-2 for the rare variants, were developed and optimized using DNA extracted from formalin-fixed paraffin-embedded tumor tissues. The simplicity of the design enables *POLE* status assessment within 4-6 hours after DNA isolation. An interlaboratory external validation study was performed to determine the practical feasibility of this assay.
Results: Cutoffs for *POLE* wild-type, *POLE*-mutant, equivocal, and failed results were predefined on the basis of a subset of *POLE* mutants and *POLE* wild-types for the internal and external validation. For equivocal cases, additional DNA sequencing is recommended. Performance in 282 EC cases, of which 99 were *POLE*-mutated, demonstrated an overall accuracy of 98.6% (95% CI, 97.2 to 99.9), a sensitivity of 95.2% (95% CI, 90.7 to 99.8), and a specificity of 100%. After DNA sequencing of 8.8% equivocal cases, the final sensitivity and specificity were 96.0% (95% CI, 92.1 to 99.8) and 100%. External validation confirmed feasibility and accuracy.
Conclusion: *QPOLE* is a qPCR assay that is a quick, simple, and reliable alternative for DNA sequencing. *QPOLE* detects all pathogenic variants in the exonuclease domain of the *POLE* gene. *QPOLE* will make low-cost *POLE*-testing available for all women with EC around the globe.

Gepubliceerd: JCO Glob Oncol. 2023;9:e2200384.
Impact factor: 4.5 ; Q onbekend

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6. Prognostic refinement of NSMP high-risk endometrial cancers using oestrogen receptor immunohistochemistry

Vermij L, Jobsen JJ, Leon-Castillo A, Brinkhuis M, Roothaan S, Powell ME, de Boer SM, Khaw P, Mileshkin LR, Fyles A, Leary A, Genestie C, Jurgenliemk-Schulz IM, Crosbie EJ, Mackay HJ, Nijman HW, Nout RA, Smit V, Creutzberg CL, Horeweg N, Bosse T, Trans PC.

Background: Risk-assessment of endometrial cancer (EC) is based on clinicopathological factors and molecular subgroup. It is unclear whether adding hormone receptor expression, L1CAM expression or CTNNB1 status yields prognostic refinement.
Methods: Paraffin-embedded tumour samples of women with high-risk EC (HR-EC) from the PORTEC-3 trial (n = 424), and a Dutch prospective clinical cohort called MST (n = 256), were used. All cases were molecularly classified. Expression of L1CAM, ER and PR were analysed by whole-slide immunohistochemistry and CTNNB1 mutations were assessed with a next-generation sequencing. Kaplan-Meier method, log-rank tests and Cox's proportional hazard models were used for survival analysis.
Results: In total, 648 HR-EC were included. No independent prognostic value of ER, PR, L1CAM, and CTNNB1 was found, while age, stage, and adjuvant chemotherapy had an independent impact on risk of recurrence. Subgroup-analysis showed that only in NSMP HR-EC, ER-positivity was independently associated with a reduced risk of recurrence (HR 0.33, 95%CI 0.15-0.75).
Conclusions: We confirmed the prognostic impact of the molecular classification, age, stage, and adjuvant CTRT in a large cohort of high-risk EC. ER-positivity is a strong favourable prognostic factor in NSMP HR-EC and identifies a homogeneous subgroup of NSMP tumours. Assessment of ER status in high-risk NSMP EC is feasible in clinical practice and could improve risk stratification and treatment.

Gepubliceerd: Br J Cancer. 2023;128(7):1360-8.
Impact factor: 8.8 ; Q1

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7. Coverage of Lateral Lymph Nodes in Rectal Cancer Patients with Routine Radiation Therapy Practice and Associated Locoregional Recurrence Rates

Sluckin TC, Hazen SJA, Horsthuis K, Beets-Tan RGH, Antonisse IE, Berbée M, van Bockel LW, Boer AH, Ceha HM, Cnossen JS, Geijsen ED, den Hartogh MD, Hendriksen EM, Intven MPW, Leseman-Hoogenboom MM, Meijnen P, Muller K, Oppedijk V, Rozema T, Rütten H, Spruit PH, Stam TC, Velema LA, Verrijssen AE, Vos-Westerman J, Tanis PJ, Marijnen CAM, Kusters M.

Purpose: Involved internal iliac and obturator lateral lymph nodes (LLNs) are a known risk factor for the occurrence of ipsilateral local recurrences (LLR) in rectal cancer. This study examined coverage of LLNs with routine radiation therapy practice in the Netherlands and associated LLR rates.
Methods and materials: Patients with a primary tumor ≤8 cm of the anorectal junction, cT3-4 stage, and at least 1 internal iliac or obturator LLN with short axis ≥5 mm who received neoadjuvant (chemo)radiation therapy, were selected from a national, cross-sectional study of patients with rectal cancer treated in the Netherlands in 2016. Magnetic resonance images and radiation therapy treatment plans were reviewed regarding segmented LLNs as gross tumor volume (GTV), location of LLNs within clinical target volume (CTV), and received proportion of the planned radiation therapy dose.
Results: A total of 223 out of 3057 patients with at least 1 LLN ≥5 mm were selected. Of those, 180 (80.7%) LLNs were inside the CTV, of which 60 (33.3%) were segmented as GTV. Overall, 202 LLNs (90.6%) received ≥95% of the planned dose. Four-year LLR rates were not significantly higher for LLNs situated outside the CTV compared with those inside (4.0% vs 12.5%, P = .092) or when receiving <95% versus ≥95% of the planned radiation therapy dose (7.1% vs 11.3%, P = .843), respectively. Two of 7 patients who received a dose escalation of 60 Gy developed an LLR (4-year LLR rate of 28.6%).
Conclusions: This evaluation of routine radiation therapy practice showed that adequate coverage of LLNs was still associated with considerable 4-year LLR rates. Techniques resulting in better local control for patients with involved LLNs need to be explored further.

Trial registration: ClinicalTrials.gov NCT05539417.

Gepubliceerd: Int J Radiat Oncol Biol Phys 2023;117(2):422-433.
Impact factor: 7.0 ; Q1

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8. Mapping the location of local and regional recurrences according to breast cancer surgery and radiation therapy: Results from EORTC 22922/10925.
Kaidar-Person O, Giasafaki P, Boersma L, De Brouwer P, Weltens C, Kirkove C, Peignaux-Casasnovas K, Budach V, van der Leij F, Vonk E, Weidner N, Rivera S, van Tienhoven G, Fourquet A, Noel G, Valli M, Guckenberger M, Koiter E, Racadot S, Abdah-Bortnyak R, Bartelink H, Struikmans H, Fortpied C, Poortmans PM; EORTC Radiation Oncology and Breast Cancer Groups.

Puropose: The purpose of this study is to evaluate the influence of the extent of surgery and radiation therapy (RT) on the rates and sites of local (LR) and regional recurrences (RR) in the EORTC 22922/10925 trial.
Patients and methods: All data were extracted from the trial's individual patients' case report forms (CRF) and analysed with a median follow-up of 15.7 years. Cumulative incidence curves were produced for LR and RR accounting for competing risks: an exploratory analysis of the effect of the extent of surgical and radiation treatments on LR rate was conducted using the Fine & Gray model accounting for competing risks and adjusted for baseline patient and disease characteristics. The significance level was set at 5%, 2-sided. Frequency tables were used to describe the spatial location of LR and RR.
Results: Out of 4004 patients included in the trial, 282 (7%) patients experienced LR and 165 (4.1%) RR, respectively. Cumulative incidence rate of LR at 15 years was lower after mastectomy (3.1%) compared to BCS + RT (7.3%) (F&G: HR (Hazard Ratio) = 0.421, 95%CI = 0.282-0.628, p-value < 0.0001). LR were similar up to 3 years for both mastectomy and BCS but continued to occur at a steady rate for BCS + RT, only. The spatial location of the recurrence was related to the locoregional therapy applied and the absolute gain of RT correlated to stage of disease and extent of surgery.
Conclusions: The extent of locoregional therapies impacts significantly on LR and RR rates and spatial location.

Gepubliceerd: Radiother Oncol 2023 Aug:185:109698.
Impact factor: 4.9 ; Q1

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9. Cosmetic Results and Side Effects of Accelerated Partial-Breast Irradiation Versus Whole-Breast Irradiation for Low-Risk Invasive Carcinoma of the Breast: The Randomized Phase III IRMA Trial.
Meduri B, Baldissera A, Lotti C, Scheijmans LJEE, Stam MR, Parisi S, Boersma LJ, Ammendolia I, Koiter E, Valli M, Scandolaro L, Busz D, Stenfert Kroese MC, Ciabatti S, Giacobazzi P, Ruggieri MP, Engelen A, Munafò T, Westenberg AH, Verhoeven K, Vicini R, D'Amico R, Lohr F, Bertoni F, Poortmans P, Frezza GP.

Purpose: The results in terms of side effects vary among the published accelerated partial-breast irradiation (APBI) studies. Here, we report the 5-year results for cosmetic outcomes and toxicity of the IRMA trial.
Methods: We ran this randomized phase III trial in 35 centers. Women with stage I-IIA breast cancer treated with breast-conserving surgery, age ≥ 49 years, were randomly assigned 1:1 to receive either whole-breast irradiation (WBI) or external beam radiation therapy APBI (38.5 Gy/10 fraction twice daily). Patients and investigators were not masked to treatment allocation. The primary end point was ipsilateral breast tumor recurrence. We hereby present the analysis of the secondary outcomes,

cosmesis, and normal tissue toxicity. All side effects were graded with the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer Radiation Morbidity Scoring Schema. Analysis was performed with both intention-to-treat and as-treated approaches.
Results: Between March 2007 and March 2019, 3,309 patients were randomly assigned to 1,657 WBI and 1,652 APBI; 3,225 patients comprised the intention-to-treat population (1,623 WBI and 1,602 APBI). At a median follow-up of 5.6 (interquartile range, 4.0-8.4) years, adverse cosmesis in the APBI patients was higher than that in the WBI patients at 3 years (12.7% *v* 9.2%; *P* = .009) and at 5 years (14% *v* 9.8%; *P* = .012). Late soft tissue toxicity (grade ≥ 3: 2.8% APBI *v* 1% WBI, *P* < .0001) and late bone toxicity (grade ≥ 3: 1.1% APBI *v* 0% WBI, *P* < .0001) were significantly higher in the APBI arm. There were no significant differences in late skin and lung toxicities.
Conclusion: External beam radiation therapy-APBI with a twice-daily IRMA schedule was associated with increased rates of late moderate soft tissue and bone toxicities, with a slight decrease in patient-reported cosmetic outcomes at 5 years when compared with WBI, although overall toxicity was in an acceptable range.
Trial registration: ClinicalTrials.gov NCT01803958.

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Impact factor: 42.1 ; Q1

Totale impact factor: 156.6
Gemiddelde impact factor: 17.4

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 8.8
Gemiddelde impact factor: 8.8

Reumatologie

1. Implementation of Recommendations on the Use of Corticosteroids in Severe COVID-19
Camirand-Lemyre F, Merson L, Tirupakuzhi Vijayaraghavan BK, Burrell AJC, Citarella BW, Domingue MP, Lévesque S, Usuf E, Wils EJ, Ohshimo S, Martin-Loeches I, Sandulescu O, Laake JH, Lamontagne F, ISARIC Clinical Characterisation 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.

Importance: Research diversity and representativeness are paramount in building trust, generating valid biomedical knowledge, and possibly in implementing clinical guidelines.
Objectives: To compare variations over time and across World Health Organization (WHO) geographic regions of corticosteroid use for treatment of severe COVID-19; secondary objectives were to evaluate the association between the timing of publication of the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial (June 2020) and the WHO guidelines for corticosteroids (September 2020) and the temporal trends observed in corticosteroid use by region and to describe the geographic distribution of the recruitment in clinical trials that informed the WHO recommendation.
Design, setting, and participants: This prospective cohort study of 434 851 patients was conducted between January 31, 2020, and September 2, 2022, in 63 countries worldwide. The data were collected under the auspices of the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC)-WHO Clinical Characterisation Protocol for Severe Emerging Infections. Analyses were restricted to patients hospitalized for severe COVID-19 (a subset of the ISARIC data set).
Exposure: Corticosteroid use as reported to the ISARIC-WHO Clinical Characterisation Protocol for Severe Emerging Infections.
Main outcomes and measures: Number and percentage of patients hospitalized with severe COVID-19 who received corticosteroids by time period and by WHO geographic region.
Results: Among 434 851 patients with confirmed severe or critical COVID-19 for whom receipt of corticosteroids could be ascertained (median [IQR] age, 61.0 [48.0-74.0] years; 53.0% male), 174 307 (40.1%) received corticosteroids during the study period. Of the participants in clinical trials that informed the guideline, 91.6% were recruited from the United Kingdom. In all regions, corticosteroid use for severe COVID-19 increased, but this increase corresponded to the timing of the RECOVERY trial (time-interruption coefficient 1.0 [95% CI, 0.9-1.2]) and WHO guideline (time-interruption coefficient 1.9 [95% CI, 1.7-2.0]) publications only in Europe. At the end of the study period, corticosteroid use for treatment of severe COVID-19 was highest in the Americas (5421 of 6095 [88.9%]; 95% CI, 87.7-90.2) and lowest in Africa (31 588 of 185 191 [17.1%]; 95% CI, 16.8-17.3).
Conclusions and relevance: The results of this cohort study showed that implementation of the guidelines for use of corticosteroids in the treatment of severe COVID-19 varied geographically. Uptake of corticosteroid treatment was lower in regions with limited clinical trial involvement. Improving research diversity and representativeness may facilitate timely knowledge uptake and guideline implementation.

Gepubliceerd: JAMA Netw Open. 2023;6(12):e2346502.
Impact factor: 13.8 ; Q1

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2. Neurological manifestations of COVID-19 in adults and children
Cho SM, White N, Premraj L, Battaglini D, Fanning J, Suen J, Bassi GL, Fraser J, Robba C, Griffee M, Singh B, Citarella BW, Merson L, Solomon T, Thomson D, ISARIC Clinical Characterisation 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.

Different neurological manifestations of coronavirus disease 2019 (COVID-19) in adults and children and their impact have not been well characterized. We aimed to determine the prevalence of neurological manifestations and in-hospital complications among hospitalized COVID-19 patients and ascertain differences between adults and children. We conducted a prospective multicentre observational study using the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) cohort across 1507 sites worldwide from 30 January 2020 to 25 May 2021. Analyses of neurological manifestations and neurological complications considered unadjusted prevalence estimates for predefined patient subgroups, and adjusted estimates as a function of patient age and time of hospitalization using generalized linear models. Overall, 161 239 patients (158 267 adults; 2972 children) hospitalized with COVID-19 and assessed for neurological manifestations and complications were included. In adults and children, the most frequent neurological manifestations at admission were fatigue (adults: 37.4%; children: 20.4%), altered consciousness (20.9%; 6.8%), myalgia (16.9%; 7.6%), dysgeusia (7.4%; 1.9%), anosmia (6.0%; 2.2%) and seizure (1.1%; 5.2%). In adults, the most frequent in-hospital neurological complications were stroke (1.5%), seizure (1%) and CNS infection (0.2%). Each occurred more frequently in intensive care unit (ICU) than in non-ICU patients. In children, seizure was the only neurological complication to occur more frequently in ICU versus non-ICU (7.1% versus 2.3%, $P < 0.001$). Stroke prevalence increased with increasing age, while CNS infection and seizure steadily decreased with age. There was a dramatic decrease in stroke over time during the pandemic. Hypertension, chronic neurological disease and the use of extracorporeal membrane oxygenation were associated with increased risk of stroke. Altered consciousness was associated with CNS infection, seizure and stroke. All in-hospital neurological complications were associated with increased odds of death. The likelihood of death rose with increasing age, especially after 25 years of age. In conclusion, adults and children have different neurological manifestations and in-hospital complications associated with COVID-19. Stroke risk increased with increasing age, while CNS infection and seizure risk decreased with age.

Gepubliceerd: Brain. 2023;146(4):1648-61.
Impact factor: 14.5 ; Q1

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3. Correction to: The effect of corticosteroids, antibiotics, and anticoagulants on the development of post-COVID-19 syndrome in COVID-19 hospitalized patients 6 months after discharge: a retrospective follow up study

Davelaar J, Jessurun N, Schaap G, Bode C, Vonkeman H.

Gepubliceerd: Clin Exp Med. 2023;23(8):4889.
Impact factor: 4.6 ; Q2

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4. The effect of corticosteroids, antibiotics, and anticoagulants on the development of post-COVID-19 syndrome in COVID-19 hospitalized patients 6 months after discharge: a retrospective follow up study

Davelaar J, Jessurun N, Schaap G, Bode C, Vonkeman H.

To assess the effect of pharmacotherapeutic interventions commonly employed in the management of COVID-19 hospitalized patients on the development of post-COVID-19 syndrome. This study employed two distinct databases, the Medisch Spectrum Twente (MST) clinical database comprising electronic health records of COVID-19 patients hospitalized at MST, and the Post-COVID cohort database which contains follow-up information on the same patients. These databases were integrated to establish the potential relationship between the administration of corticosteroids, antibiotics, or anticoagulants during hospitalization and the occurrence of post-COVID-19 syndrome

after a 6-month interval following discharge. A total of 123 patients who were hospitalized due to COVID-19 infection were included in this study. Among these patients, 33 (26.8%) developed post-COVID-19 syndrome which persisted even 6 months after hospital discharge. Multivariate analysis revealed that patients who received treatment with corticosteroids had a significantly lower likelihood (OR 0.32, 95% CI 0.11-0.90) of developing post-COVID-19 syndrome, while no significant association was observed for treatment with antibiotics (OR 1.26, 95% CI 0.47-3.39) or anticoagulants (OR 0.55, 95% CI 0.18-1.71). The findings of this study indicate that corticosteroids exert a significant protective effect against the development of post-COVID-19 syndrome in patients who were hospitalized due to COVID-19 infection. Although a trend towards a protective effect of anticoagulants was observed, it did not reach statistical significance. On the contrary, patients treated with antibiotics were shown to have increased chances of developing post-COVID-19 syndrome, although this effect was also not statistically significant.

Gepubliceerd: Clin Exp Med. 2023;23(8):4881-8.
Impact factor: 4.6 ; Q2

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5. Analysis and visualization of the course and burden over time of adverse drug reactions (ADRs) attributed to TNFα-inhibitors in patients with inflammatory rheumatic diseases (IRDs)
de Boer M, Gosselt HR, Jansen J, van Doorn MBA, Hoentjen F, Nurmohamed MT, Spuls PI, Tas SW, Vonkeman HE, Jessurun NT.

Background: We aimed to investigate course and burden over time of ADRs attributed to TNFα-inhibitors in IRD-patients, and whether Sankey diagrams and polar plots can visualize this.
Research design and methods: Data on ADRs experienced during the Dutch Biologic Monitor (January 2017 till December 2022) were used in this study. We selected IRD-patients using a TNFα-inhibitor, reporting skin reactions/infections/injection site reactions and completing ≥3 questionnaires (i.e. the initial report and ≥2 follow-ups). Course was scored as worsening/improving/remaining stable/resolving and as (non-)recurrent. Patients scored burden from 1 (no burden) to 5 (very high burden). Sankey diagrams and polar plots visualized this.
Results: 202 patients were included, reporting 353 ADRs. Most skin reactions were stable (25.0%). Most infections resolved (50.8%). Injection site reactions were mostly recurrent (72.3%). Skin reactions and infections tended to decrease in burden . Infections had highest burden at start, which mostly decreased over time. Injection site reactions had a low and stable burden.
Conclusions: Skin reactions attributed to TNFα-inhibitors by IRD-patients are stable with a slightly decreasing burden over time. Infections have highest burden at start but resolved mostly. Injection site reactions have a low and stable burden. Sankey diagrams and polar plots are suitable to visualize this.

Gepubliceerd: Expert Opin Drug Saf. 2023;22(3):195-202.
Impact factor: 3.1 ; Q3

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6. The impact of health literacy: associations with disease activity and medication prescription in patients with rheumatoid arthritis
Gorter A, Bakker MM, Ten Klooster PM, Boonen A, Vonkeman HE.

Objective: The aim of this study was to explore the longitudinal associations between health literacy profiles and disease activity and medication prescription in patients with RA.
Methods: Patients with RA who previously completed the Health Literacy Questionnaire (HLQ) and were assigned 1 of 10 distinct health literacy profiles based on cluster analysis were further

aggregated into three groups: 'several health literacy limitations', 'some health literacy limitations' and 'good health literacy'. Linear mixed modelling (LMM) was used to analyse the association between health literacy groups and disease activity over the course of 1 year. Chi-squared tests and logistic regression analyses were used to compare medication prescriptions between the groups.
Results: A total of 108 patients with RA were included. LMM showed a significant effect of health literacy group on disease activity over time (P = 0.010). Patients with 'good health literacy' had significantly lower disease activity over time [28-joint DAS with ESR (DAS28-ESR) = 2.4] than patients with 'several health literacy limitations' (DAS28-ESR = 3.1), independent of age, gender and education level. Patients with 'good health literacy' were most often prescribed a biologic DMARD (50%), whereas patients with 'some health literacy limitations' more commonly received a conventional synthetic DMARD only [72.7%; odds ratio (OR) 4.24], and patients with 'several health literacy limitations' were more often prescribed prednisolone (52.4%; OR 3.56).
Conclusion: Significant differences in longitudinal disease activity and medication prescription were observed between groups with different health literacy levels. These results stress the importance of insights into the role of health literacy in treatment and outcomes in patients with RA.

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Impact factor: 5.5 ; Q1

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7. Sex differences in adverse drug reactions from Adalimumab and etanercept in patients with inflammatory rheumatic diseases
Gosselt HR, van Lint JA, Kosse LJ, Spuls PI, Vonkeman HE, Tas SW, Hoentjen F, Nurmohamed MT, van den Bemt BJF, van Doorn MBA, Jessurun NT.

Background: We examine sex differences in relation to the nature, frequency, and burden of patient-reported adverse drug reactions (ADRs) in patients with inflammatory rheumatic diseases.
Research design and methods: Rheumatoid arthritis, psoriatic arthritis, or axial spondyloarthritis patients using etanercept or adalimumab from the Dutch Biologic Monitor were sent bimonthly questionnaires concerning experienced ADRs. Sex differences in the proportion and nature of reported ADRs were assessed. Additionally, 5-point Likert-type scales reported for the burden of ADRs, were compared between sexes.
Results: In total 748 consecutive patients were included (59% female). From the women 55% reported ≥1 ADR, which was significantly higher than 38% of the men that reported ≥1 ADR ($p < 0.001$). A total of 882 ADRs were reported comprising 264 distinct ADRs. The nature of the reported ADRs differed significantly between both sexes ($p = 0.02$). Women in particular reported more injection site reactions than men. The burden of ADRs was similar between sexes.
Conclusions: Sex differences in the frequency and nature of ADRs, but not in ADR burden, exist during treatment with adalimumab and etanercept in patients with inflammatory rheumatic diseases. This should be taken into consideration when investigating and reporting results on ADRs and when counseling patients in daily clinical practice.

Gepubliceerd: Expert Opin Drug Saf. 2023;22(6):501-7.
Impact factor: 3.1 ; Q3

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8. Thrombotic and hemorrhagic complications of COVID-19 in adults hospitalized in high-income countries compared with those in adults hospitalized in low- and middle-income countries in an international registry
Griffee MJ, Bozza PT, Reyes LF, Eddington DP, Rosenberger D, Merson L, Citarella BW, Fanning JP, Alexander PMA, Fraser J, Dalton H, Cho SM, ISARIC Clinical Characterisation 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: COVID-19 has been associated with a broad range of thromboembolic, ischemic, and hemorrhagic complications (coagulopathy complications). Most studies have focused on patients with severe disease from high-income countries (HICs).
Objectives: The main aims were to compare the frequency of coagulopathy complications in developing countries (low- and middle-income countries [LMICs]) with those in HICs, delineate the frequency across a range of treatment levels, and determine associations with in-hospital mortality.
Methods: Adult patients enrolled in an observational, multinational registry, the International Severe Acute Respiratory and Emerging Infections COVID-19 study, between January 1, 2020, and September 15, 2021, met inclusion criteria, including admission to a hospital for laboratory-confirmed, acute COVID-19 and data on complications and survival. The advanced-treatment cohort received care, such as admission to the intensive care unit, mechanical ventilation, or inotropes or vasopressors; the basic-treatment cohort did not receive any of these interventions.
Results: The study population included 495,682 patients from 52 countries, with 63% from LMICs and 85% in the basic treatment cohort. The frequency of coagulopathy complications was higher in HICs (0.76%-3.4%) than in LMICs (0.09%-1.22%). Complications were more frequent in the advanced-treatment cohort than in the basic-treatment cohort. Coagulopathy complications were associated with increased in-hospital mortality (odds ratio, 1.58; 95% CI, 1.52-1.64). The increased mortality associated with these complications was higher in LMICs (58.5%) than in HICs (35.4%). After controlling for coagulopathy complications, treatment intensity, and multiple other factors, the mortality was higher among patients in LMICs than among patients in HICs (odds ratio, 1.45; 95% CI, 1.39-1.51).
Conclusion: In a large, international registry of patients hospitalized for COVID-19, coagulopathy complications were more frequent in HICs than in LMICs (developing countries). Increased mortality associated with coagulopathy complications was of a greater magnitude among patients in LMICs. Additional research is needed regarding timely diagnosis of and intervention for coagulation derangements associated with COVID-19, particularly for limited-resource settings.

Gepubliceerd: Res Pract Thromb Haemost. 2023;7(5):102142.
Impact factor: 4.6 ; Q2

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9. Effectiveness and cost-effectiveness of combined asynchronous telemonitoring and patient-initiated care for spondyloarthritis: protocol for a pragmatic multicentre randomised controlled trial (TeleSpA Study)
Hermans K, Boonen A, Vonkeman HE, van Tubergen A.

Introduction: During the COVID-19 pandemic, an accelerated uptake of remote monitoring strategies, replacing traditional face-to-face care, has been observed. However, data on the effects of remote care interventions for patients with rheumatic and musculoskeletal diseases remain scarce and interpretation is hampered by study heterogeneity and research quality concerns. High-quality evidence is required to guide future implementation in clinical practice, with health economic analyses identified as an important knowledge gap. Randomised controlled trials (RCTs) comparing telemonitoring with conventional care for patients with spondyloarthritis (SpA) are currently lacking.
Methods and analysis: TeleSpA is a pragmatic, multicentre RCT investigating the effectiveness and cost-effectiveness of combined asynchronous telemonitoring and patient-initiated follow-up for patients with SpA, compared with conventional care. Two-hundred patients will be recruited at two hospitals and randomised (1:1) to the study intervention or standard care. The primary endpoint is a reduction in the number of follow-up visits by ≥25% in the intervention compared with standard care group, during a 1-year period. Secondary endpoints are (a) non-inferiority of the study intervention

with regard to health outcomes, quality of care and patient-reported experience with care; and (b) cost-effectiveness of the intervention, evaluated through a prospective trial-based cost-utility analysis. In addition, experiences with the study intervention will be assessed among patients and healthcare providers, and factors associated with primary and secondary endpoints will be identified. **Ethics and dissemination:** This study was approved by the Medical Research Ethics Committee of the Academic Hospital Maastricht/Maastricht University (NL71041.068.19/METC 19-059). Results will be disseminated through publications in peer-reviewed journals and conference presentations.

Gepubliceerd: BMJ Open. 2023;13(2):e067445.
Impact factor: 2.9 ; Q2

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10. The Relationship between Nociceptive Detection Thresholds and Pressure- and Electrical Pain Thresholds: An Explorative Study in Rheumatoid Arthritis Patients
Jansen N, Berfelo T, Vonkeman HE, Ten Klooster PM, van Den Berg B, Krabbenbos IP, Buitenweg JR.

Recently, methods have been developed enabling the characterization of the nociceptive function at the detection threshold level by measuring nociceptive detection thresholds (NDTs), rather than at the level of the pain threshold via pain threshold (PT) measurements. Both NDT and PT measurements aim to characterize (parts of) the nociceptive system. To date it is unclear if, and if so to what extent, the two outcomes relate to one another. In this study, the primary aim is to explore the relationship between the two measures in patients with rheumatoid arthritis (RA). As secondary aim, we explore differences in NDT between these RA patients with age- and sex-matched healthy controls (HC) from a readily existing dataset. In total 46 RA patients have been recruited, whereby the pressure- (PPT; bilaterally at two locations) and electrical (EPT) pain threshold were evaluated, as well as the NDTs. Significant, positive correlations were found between the EPT and PPT (R=0.54-0.60), but not with the NDTs (R≤0.25). As compared to HC, higher NDTs were found in the RA group. As the presence of a statistically significant weak relationship can only be evaluated using a larger sample size, our results indicate that there is no moderate or stronger relation between PT and NDT outcomes. This implicates that the two outcomes are not strongly driven by the same (nociceptive) mechanism(s). Future research into NDTs and what factors and/or mechanisms affect the outcome, could yield relevant insights into how to use and interpret the results of this relatively new method.Clinical Relevance - The evaluation of nociceptive detection thresholds, in isolation or together with conventionally evaluated pain thresholds, might provide valuable and complementary insights into nociceptive (dis)function in man.

Gepubliceerd: Annu Int Conf IEEE Eng Med Biol Soc. 2023;2023:1-4.
Impact factor: onbekend

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11. Test-Retest Reliability of the Generalized Pain Questionnaire in Patients with Rheumatoid Arthritis and Preliminary Reference Values for Non-Clinical and Several Clinical Samples
Jansen N, Ten Klooster PM, Vonkeman HE, Buitenweg JR.

Introduction: Generalized pain hypersensitivity is a characteristic feature in many different types of chronic pain. Recently, a 7-item self-reported Generalized Pain Questionnaire (GPQ) was developed to evaluate the presence and severity of generalized pain hypersensitivity in chronic pain patients. Here, we evaluate the test-retest reliability of the GPQ and report on preliminary reference values for various patient groups and healthy subjects.
Methods: Eighty-five patients diagnosed with Rheumatoid Arthritis (RA) completed the GPQ twice over a 2-week interval. Relative and absolute indicators of reliability were determined using data of

69 patients (81.2% retest response rate). Using readily available datasets, preliminary reference data were established in two nonclinical populations (NCP1; N = 30 and NCP2; N = 111), and for patients diagnosed with RA (N = 114), gout (N = 97), fibromyalgia (N=98), or neuropathy (N = 25), or participants in a pain rehabilitation program (N = 33).
Results: Total GPQ scores had an ICC of 0.78 (95% CI: 0.67 to 0.86). While no systematic or proportional differences were found for the GPQ total score; two (near-)significant systematic differences were observed for the individual questions. The standard error of measurement and minimal detectable change were 2.22 and 6.2, respectively. Mean ± SD scores were found to be 0.8 ± 1.2 (NCP1), 4.0 ± 4.6 (NCP2), 6.4 ± 5.5 (Gout), 6.5 ± 5.1 (RA), 8.1 ± 4.5 (Neuropathy), 13.6 ± 4.0 (Rehabilitation) and 16.0 ± 5.0 (Fibromyalgia).
Discussion: This study shows that the GPQ has acceptable reliability to be used as a tool to evaluate the presence and intensity of generalized pain hypersensitivity. The absolute measures of reliability and the preliminary reference values reported here aid in the interpretation of future studies with the GPQ.

Gepubliceerd: J Pain Res. 2023;16:4127-37.
Impact factor: 2.7 ; Q3

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12. Further evaluation of inflammatory and non-inflammatory aspects of pain in rheumatoid arthritis patients
Jansen N, Ten Klooster PM, Vonkeman HE, van den Berg B, Buitenweg JR.

Objective: A high discrepancy between the number of tender and swollen joints (e.g. ΔTSJ ≥ 7) has previously been used as an indication for the presence of changes in central mechanisms in patients with moderate-to-high disease activity. In this study, we explored whether the ΔTSJ can also be used to obtain insights into the underlying pain mechanisms in patients with on average well-controlled disease activity.
Methods: A 2 year retrospective analysis of routinely obtained 28-joint DAS (DAS28) components was performed on 45 patients with low inflammatory activity at the group level. All patients underwent pressure pain threshold (PPT) and electrical pain threshold (EPT) measurements and completed four self-report questionnaires [short-form 36 (SF-36v2); central sensitization inventory (CSI); generalized pain questionnaire (GPQ); and the pain catastrophizing scale (PCS)].
Results: Patients with a ΔTSJ ≥ 3 at least once in the past 2 years showed significantly lower EPT and PPT values and higher levels of pain and disability on the SF-36v2 compared with the ΔTSJ < 3 group. Furthermore, GPQ scores were significantly higher in those with ΔTSJ ≥ 3, while CSI and PCS scores were similar.
Conclusion: These findings suggest that in patients in the ΔTSJ ≥ 3 group, mechanisms other than inflammation (only) underlie the pain. Moreover, our findings suggest that among the multiple potential underlying psychological mechanisms, pain catastrophizing (as measured by the PCS) and psychological hypervigilance (as measured by the CSI) do not play an important role. These findings could be useful in the clinical management of the patient. Depending on the dominant mechanism underlying the (persistent) pain, patients might respond differently to treatment.

Gepubliceerd: Rheumatol Adv Pract. 2023;7(3):rkad076.
Impact factor: 3.1 ; Q onbekend

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13. Characteristics and outcomes of an international cohort of 600 000 hospitalized patients with COVID-19

Kartsonaki C, Baillie JK, Barrio NG, Baruch J, Beane A, Blumberg L, Bozza F, Broadley T, Burrell A, Carson G, Citarella BW, Dagens A, Dankwa EA, Donnelly CA, Dunning J, Elotmani L, Escher M, Farshait N, Goffard JC, Gonçalves BP, Hall M, Hashmi M, Sim Lim Heng B, Ho A, Jassat W, Pedrera Jiménez M, Laouenan C, Lissauer S, Martin-Loeches I, Mentré F, Merson L, Morton B, Munblit D, Nekliudov NA, Nichol AD, Singh Oinam BC, Ong D, Panda PK, Petrovic M, Pritchard MG, Ramakrishnan N, Ramos GV, Roger C, Sandulescu O, Semple MG, Sharma P, Sigfrid L, Somers EC, Streinu-Cercel A, Taccone F, Vecham PK, Kumar Tirupakuzhi Vijayaraghavan B, Wei J, Wils EJ, Ci Wong X, Horby P, Rojek A, Olliaro PL, ISARIC Clinical Characterisation 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: We describe demographic features, treatments and clinical outcomes in the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) COVID-19 cohort, one of the world's largest international, standardized data sets concerning hospitalized patients.
Methods: The data set analysed includes COVID-19 patients hospitalized between January 2020 and January 2022 in 52 countries. We investigated how symptoms on admission, co-morbidities, risk factors and treatments varied by age, sex and other characteristics. We used Cox regression models to investigate associations between demographics, symptoms, co-morbidities and other factors with risk of death, admission to an intensive care unit (ICU) and invasive mechanical ventilation (IMV).
Results: Data were available for 689 572 patients with laboratory-confirmed (91.1%) or clinically diagnosed (8.9%) SARS-CoV-2 infection from 52 countries. Age [adjusted hazard ratio per 10 years 1.49 (95% CI 1.48, 1.49)] and male sex [1.23 (1.21, 1.24)] were associated with a higher risk of death. Rates of admission to an ICU and use of IMV increased with age up to age 60 years then dropped. Symptoms, co-morbidities and treatments varied by age and had varied associations with clinical outcomes. The case-fatality ratio varied by country partly due to differences in the clinical characteristics of recruited patients and was on average 21.5%.
Conclusions: Age was the strongest determinant of risk of death, with a ∼30-fold difference between the oldest and youngest groups; each of the co-morbidities included was associated with up to an almost 2-fold increase in risk. Smoking and obesity were also associated with a higher risk of death. The size of our international database and the standardized data collection method make this study a comprehensive international description of COVID-19 clinical features. Our findings may inform strategies that involve prioritization of patients hospitalized with COVID-19 who have a higher risk of death.

Gepubliceerd: Int J Epidemiol. 2023;52(2):355-76.
Impact factor: 7.7 ; Q1

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14. Disease-specific ADRs of TNF-α inhibitors as reported by patients with inflammatory rheumatic diseases: a registry-based prospective multicenter cohort study
Roest LH, Kosse LJ, van Lint JA, Gosselt HR, Scholl JHG, van Puijenbroek E, Vonkeman HE, Tas SW, Nurmohamed MT, van den Bemt BJF, Jessurun NT.

Background: The extent to which adverse drug reactions (ADRs) of biologics differ per immune-mediated inflammatory disease (IMID), and the relevance of tailoring ADR information per IMID is not fully investigated. We aimed to compare patient-reported ADRs attributed to adalimumab and etanercept between different inflammatory rheumatic diseases (IRDs).
Research design and methods: ADR reports from IRD patients were extracted from the Dutch Biologic Monitor. ADR frequencies were compared using Fischer-Freeman-Halton exact test and the influence of covariates was assessed using binomial logistic regression.
A total, of 729 participants were included, of which 354 participants reported 887 unique ADRs. ADR frequencies were not significantly different between the IRDs. Rheumatoid arthritis and ankylosing spondylitis including axial spondyloarthritis patients had an increased risk of ADRs related to

'Respiratory, thoracic and mediastinal disorders' and as compared to psoriatic arthritis patients. Etanercept use, combination therapy with methotrexate and/or corticosteroids, and age also influenced the risk of reporting specific ADRs.
Conclusions: There were no differences in frequencies and nature of patient-reported ADRs attributed to adalimumab and etanercept between different IRDs. However, more research is needed to align patients' and health-care professionals' perspectives to improve knowledge on disease-specific ADRs.

Gepubliceerd: Expert Opin Drug Saf. 2023;22(3):203-11.
Impact factor: 3.1 ; Q3

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15. Recurring Fatigue After Biologic Administration: Patient-Reported Data from the Dutch Biologic Monitor
van Lint JA, Jessurun NT, Tas SW, Vonkeman HE, van Doorn MBA, Hoentjen F, Nurmohamed MT, van Puijenbroek EP, van den Bemt BJF.

Background: Fatigue is a common problem in immune-mediated inflammatory disease (IMID) patients, significantly impacting their quality of life.
Objectives: In this study, we describe the pattern and characteristics of fatigue as a patient-reported adverse drug reaction (ADR) of biologics, and compared patient and treatment characteristics with patients reporting other ADRs or no ADRs.
Methods: In this cohort event monitoring study, the description and characteristics of fatigue reported as a possible ADR in the Dutch Biologic Monitor were assessed and analysed for commonly recurring themes or patterns. Baseline and treatment characteristics of patients with fatigue and patients reporting other ADRs or no ADRs were compared.
Results: Of 1382 participating patients, 108 patients (8%) reported fatigue as an ADR of a biologic. Almost half of these patients (50 patients, 46%) described episodes of fatigue during or shortly after biologic injection, which often recurred following subsequent injections. Patients with fatigue were significantly younger than patients with other ADRs or patients without ADRs (median age for patients with fatigue, 52 years; median age for patients with other ADRs, 56 years; and median age for patients without ADRs, 58 years); significantly more often smoked (25% vs. 16% and 15%); used infliximab (22% vs. 9% and 13%), rituximab (9% vs. 3% and 1%) or vedolizumab (6% vs. 2% and 1%); and significantly more often had Crohn's disease (28% vs. 13% and 13%) and other comorbidities (31% vs. 20% and 15%). Patients with fatigue significantly less frequently used etanercept (12% vs. 29% and 34%) or had rheumatoid arthritis (30% vs. 45% and 43%).
Conclusions: IMID patients may experience fatigue as a postdosing effect of biologics.

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Impact factor: 6.8 ; Q1

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16. Development of a Framework Structuring Themes in the Course of Adverse Drug Reactions from a Patient's Perspective
van Lint JA, Sonnenberg M, Vonkeman HE, van den Bemt BJF, van Puijenbroek EP, Jessurun NT.

Introduction: There is a need for more extensive information about adverse drug reactions (ADRs) for patients than currently available, including information on the course of ADRs. Aspects characterising the course of ADRs from the patient perspective have not been identified before.
Objective: We aimed to develop a framework based on common themes in the course of ADRs identified from patient descriptions in patient-reported ADRs.

Methods: In this qualitative study, patient descriptions of the course of patient-reported ADRs were analysed by a thematic analysis with an inductive approach using three different existing datasets containing patient-reported ADRs. Two datasets included patient-reported ADRs from cohort event monitoring of biologics and direct oral anticoagulants and one dataset included spontaneous reports from patients concerning medication for lower urinary tract symptoms. A conceptual framework was developed from the identified main themes and subthemes.
Results: Patient-reported data concerning 3888 ADRs were analysed. Six main themes with multiple subthemes were identified from patient descriptions of the course of ADRs. Four themes were descriptive: frequency of an ADR episode, duration of an ADR episode, moment or period of ADR occurrence, and development in the intensity of the ADR. Two themes concerned factors influencing the course of ADRs: triggering factors and improving factors.
Conclusions: The presented framework illustrates that patients describe extensive details on the course and timeframe of ADRs. The identified themes provide a basis for improving the systematic data collection of more extensive details about ADRs from patients as a first step towards the provision of more comprehensive ADR information to patients.

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Impact factor: 4.2 ; Q2

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17. First-time adverse drug reactions, survival analysis, and the share of adverse drug reactions in treatment discontinuation in real-world rheumatoid arthritis patients: a comparison of first-time treatment with adalimumab and etanercept
Velthuis K, Jessurun NT, Nguyen TDM, Scholl J, Jansen JRG, van Lint JA, Kosse LJ, Ten Klooster PM, Vonkeman HE.

Background: This study aims to compare nature and frequency of adverse drug reactions (ADRs), time to first ADR, drug survival, and the share of ADRs in treatment discontinuation of first-time treatment with adalimumab (ADA) and etanercept (ETN) in real-world RA patients.
Research design and methods: Retrospective, single-center cohort study including naïve patients treated between January 2003-April 2020. Time to first ADR and drug survival of first-time treatment were studied using Kaplan-Meier and Cox-regression models up to 10 years, with 2- and 5-year post-hoc sensitivity analysis. Nature and frequencies of first-time ADRs and causes of treatment discontinuation were assessed.
Results: In total, 416 patients (ADA: 255, ETN: 161, 4865 patient years) were included, of which 92 (22.1%) experienced ADR(s) (ADA: 59, 23.1%; ETN: 33, 20.4%). Adjusted for age, gender and concomitant conventional DMARD use, ADA was more likely to be discontinued than ETN up to 2-, 5- and 10-year follow-up (adjusted HRs 1.63; 1.62; 1.59 (all $p<0.001$)). ADRs were the second reason of treatment discontinuation (ADA 20.7%, ETN 21.4%).
Conclusions: Despite seemingly different nature and frequencies, ADRs are the second reason of treatment discontinuation for both bDMARDs. Furthermore, 2-, 5-, and 10-year drug survival is longer for ETN compared to ADA.
Keywords: Rheumatoid arthritis; adverse drug reactions; bDMARDs; biologicals; drug survival; real-world data.

Gepubliceerd: Expert Opin Drug Saf. 2023;22(6):485-92.
Impact factor: 3.1 ; Q3

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18. Impact of adverse drug reactions on the treatment pathways of early rheumatoid arthritis patients: a prospective observational cohort study

Velthuis K, Poppelaars F, Ten Klooster PM, Vonkeman HE, Jessurun NT.

Background: Several patient characteristics may be of influence on treatment pathways of rheumatoid arthritis (RA) patients in clinical practice. The aim of this study is to analyze treatment pathways of early RA patients stratified for gender and adverse drug reaction (ADR) occurrence.
Research design and methods: Treatment pathways of patients included in the DREAM-RA treat-to-target cohort I between 16th of July 2006-30th of April 2020 were assessed. Treatment pathways were visualized in Sankey diagrams. Follow-up time, duration per treatment and the number of treatments received were stratified for gender and ADR occurrence and analyzed. Independent t-tests and chi-square tests were performed where applicable.
Results: Treatment pathways of 372 patients (follow-up: 2488.4 years, mean 6.7 ± 3.7 years) were analyzed. The Sankey diagrams visualize that treatment pathways became increasingly varied and complex over time. No significant differences were found when comparing female patients and male patients. However, the average treatment duration was shorter in patients with ADRs (1.8 vs. 2.7 years, $p < 0.05$), and the number of treatments higher (3.5 vs. 2.5, $p < 0.05$).
Conclusions: Treatment pathways increase in complexity over time. Differences were found between patients with and without ADRs, with patients that experience ADRs receiving more and shorter treatments.

Gepubliceerd: Expert Opin Drug Saf. 2023;22(8):753-62.
Impact factor: 3.1 ; Q3

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19. Association of Country Income Level With the Characteristics and Outcomes of Critically Ill Patients Hospitalized With Acute Kidney Injury and COVID-19

Wainstein M, Spyrison N, Dai D, Ghadimi M, Chávez-Iñiguez JS, Rizo-Topete L, Citarella BW, Merson L, Pole JD, Claure-Del Granado R, Johnson DW, Shrapnel S, ISARIC Clinical Characterisation 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.

Introduction: Acute kidney injury (AKI) has been identified as one of the most common and significant problems in hospitalized patients with COVID-19. However, studies examining the relationship between COVID-19 and AKI in low- and low-middle income countries (LLMIC) are lacking. Given that AKI is known to carry a higher mortality rate in these countries, it is important to understand differences in this population.
Methods: This prospective, observational study examines the AKI incidence and characteristics of 32,210 patients with COVID-19 from 49 countries across all income levels who were admitted to an intensive care unit during their hospital stay.
Results: Among patients with COVID-19 admitted to the intensive care unit, AKI incidence was highest in patients in LLMIC, followed by patients in upper-middle income countries (UMIC) and high-income countries (HIC) (53%, 38%, and 30%, respectively), whereas dialysis rates were lowest among patients with AKI from LLMIC and highest among those from HIC (27% vs. 45%). Patients with AKI in LLMIC had the largest proportion of community-acquired AKI (CA-AKI) and highest rate of in-hospital death (79% vs. 54% in HIC and 66% in UMIC). The association between AKI, being from LLMIC and in-hospital death persisted even after adjusting for disease severity.
Conclusions: AKI is a particularly devastating complication of COVID-19 among patients from poorer nations where the gaps in accessibility and quality of healthcare delivery have a major impact on patient outcomes.

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Impact factor: 6.0 ; Q1

20. Factors Associated With Residual Disease in Axial Spondyloarthritis: Results From a Clinical Practice Registry
Webers C, Boonen A, Vonkeman HE, van Tubergen A.

Objective: To explore residual disease, defined as substantial symptoms and disease burden despite a remission or low disease activity (LDA) state, in patients with axial spondyloarthritis (axSpA), and to determine which factors are associated with residual disease.
Methods: For this cross-sectional observational study, 1 timepoint per patient was used from SpA-Net, a web-based monitoring registry for SpA. Patients with an Ankylosing Spondylitis Disease Activity Score (ASDAS) < 2.1 (LDA) were included. Indicators of residual disease (outcomes) included fatigue (primary outcome), pain, physical functioning, health-related quality of life (HRQOL), and peripheral symptoms. Sex was the primary explanatory factor for residual disease. Other explanatory factors included demographics and disease-related factors. Associations between these factors and presence and extent of residual disease were explored using logistic and linear regression.
Results: In total, 267 patients in an LDA state were included. Mean age was 50.6 (SD 14.3) years and 100 (37.5%) were female. Residual disease occurred frequently (n = 114 [42.7%] had fatigue scores > 4/10; n = 34 [17.8%] had pain scores > 4/10), including in those in remission (ASDAS < 1.3). Physical HRQOL was reduced in 27% and moderate/poor in 33%. Multivariable regression analyses showed that reported fatigue was more severe and prevalent in female patients (fatigue severity [0-10]: B_{female} = 0.78, 95% CI 0.18-1.38; fatigue > 4/10: OR_{female} = 3.29, 95% CI 1.74-6.20). Other indicators of residual disease (ie, pain, peripheral symptoms, physical HRQOL) were also more severe and/or more prevalent in females.
Conclusion: Residual disease is frequent in patients with axSpA who are in an LDA state, including remission, and it is particularly prevalent in female patients. Future studies should address how to manage or prevent residual disease in axSpA.

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Impact factor: 3.9 ; Q2

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21. Factors associated with treatment intensification in patients with axial spondyloarthritis and high disease activity in clinical practice
Webers C, El-Din RN, Beckers E, Been M, Vonkeman HE, van Tubergen A.

Objective: To investigate which factors are associated with treatment intensification (TI) in axial spondylarthritis (axSpA) patients with high disease activity (HDA).
Methods: Patients with axSpA and HDA (Ankylosing Spondylitis Disease Activity Score [ASDAS]≥2.1) from the Dutch SpA-Net registry were included. TI was defined as: 1) higher dose or shorter interval of the same drug, 2) switch from current drug to another due to inefficacy, or 3) addition of a new drug. Only anti-inflammatory drugs were considered. Primary determinants considered were ASDAS, Assessment of SpondyloArthritis international Society Health Index (ASAS HI) and physician global (PhGA). Acceptable symptom state according to patient (PASS-patient) or physician (PASS-physician) were included in sensitivity analyses. Patient-centered and physician-centered logistic regression models were used to investigate the association between potential determinants and TI.
Results: In total, 121 patients with HDA were included. TI was conducted in a minority (41/121, 33.9%), and mainly involved a switch or addition of a drug. In multivariable regression analyses, a higher ASDAS was associated with TI in the patient-centered model (ORASDAS = 1.94, [95%CI 1.00-3.74]). However, in the physician-centered model, this association attenuated, and PhGA or PASS-physician were the primary factors associated with TI (ORPhGA = 1.71 [1.24-2.34]; ORPASS-physician

= 94.95). Interestingly, patient-centered factors (ASAS HI/PASS-patient/education level) did not contribute to TI.
Conclusion: In practice, treatment is intensified in a minority of axSpA patients with HDA. Physician-centered factors are associated with the decision to change treatment, independently of disease activity or patient perspective. Further research is needed to better understand these decisions.

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Impact factor: 5.5 ; Q1

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22. 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.

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Impact factor: 4.7 ; Q2

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23. Patients' and health-care professionals' perspectives on adverse drug reaction burden attributed to the use of biological DMARDs: a qualitative study
Westerink HJ, Kosse LJ, Jessurun NT, Tubergen AV, Vonkeman HE, Nurmohamed MT, van den Bemt BJF, de Vries M.

Background: Previous studies showed a discrepancy between health-care professionals' (HCPs') and patients' perspective on adverse drug reaction (ADR) burden. However, it is unclear which factors make an ADR burdensome. We aimed to give insight into why ADRs are perceived as burdensome by inflammatory rheumatic disease (IRD) patients, and whether this differs from the HCPs' perspective.
Research design and methods: A qualitative study was conducted using Dutch Biologic Monitor data. Participants received bimonthly questionnaires on experienced ADRs attributed to biological DMARDs and were asked to elaborate on ADR burden using a Likert-type scale and an open-ended question for clarification. Data of 440 IRD patients were analyzed following thematic analysis. A similar analysis was done with semi-structured interviews with 13 HCPs.

Results: We identified seven themes associated with ADR burden: 'effect on medication prescription,' 'impact on appearance,' 'impact on autonomy,' 'impact on daily life,' 'psychological consequences,' 'distressing aspects of ADR,' and 'physical consequences.' Identical themes were identified by HCPs, although they identified most subthemes in 'psychological consequences,' and less subthemes in 'impact on daily life' and 'impact on autonomy.'
Conclusion: Patients describe perceived ADR burden in both physical and psychological themes. The HCPs' perspective is comparable, but mostly focuses on psychological impact.

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Impact factor: 3.1 ; Q3

Totale impact factor: 113.7
Gemiddelde impact factor: 4.9

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 4
Totale impact factor: 17.8
Gemiddelde impact factor: 4.5

Thoraxcentrum Twente

1. Multicentre experience with valve-sparing aortic root replacement by means of combined remodelling and external aortic ring annuloplasty in patients with Marfan syndrome
Accord RE, Mecozzi G, Aalberts JJJ, Nijs J, Ter Weeme M, van Aarnhem E, Mariani MA, van den Berg MP.

Objectives: The most recent valve-sparing root replacement technique combines the advantages of the reimplantation (David) and remodelling (Yacoub) techniques. The aortic root is reconstructed according to the remodelling technique, the aortic valve is repaired according to the principle of effective height, and an external ring provides annular support. The purpose of this study was to evaluate operative and mid-term outcomes using this technique in patients with Marfan syndrome.
Methods: Adult patients with Marfan syndrome who had an indication for aortic root surgery according to European Society of Cardiology guidelines and were operated on using this new root replacement technique were retrospectively evaluated. Follow-up was obtained from standard outpatient visits and included echocardiography.
Results: The study group comprised 22 patients (mean age 36 years, 68% males). Mean follow-up was 7.5 years. There were no mortalities. Two patients required aortic valve replacement because of aortic regurgitation. In both patients, the aortic root was severely dilated (≥65 mm) preoperatively, with grade III aortic valve regurgitation and aortic valve cusps that were very fragile. Aortic regurgitation was grade ≤I on follow-up in 18 of the remaining 20 patients.
Conclusions: Valve-sparing root replacement using remodelling combined with aortic-ring annuloplasty is safe in patients with Marfan syndrome. The mid-term outcome is promising in patients undergoing elective valve-sparing root replacement at recommended root diameters. However, in patients with extremely dilated aortic roots and already severe aortic regurgitation, the technique should be used cautiously as aortic cusps are fragile and might not be suitable for durable repair.

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Impact factor: onbekend

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2. Virtual reality simulation as a training tool for perfusionists in extracorporeal circulation: Establishing face and content validity
Babar ZUD, Max SA, Martina BG, Rosalia RA, Peek JJ, van Dijk A, Sadeghi AH, Mahtab EAF.

Objective: We conducted a prospective study to assess the face and content validity of a new virtual reality (VR) extracorporeal circulation simulator (ECC) developed for perfusionists to facilitate training and practice. We evaluated the opinions of students and staff members about the feasibility of the simulation. The 2 groups consisted of experts (qualified perfusionists) and novices (trainee perfusionists).
Methods: Perfusionists (n = 12 experts and n = 11 trainees) received instructions on how to use the VR simulator and then proceeded to perform the start of cardiopulmonary bypass in the VR environment. Participants then completed a Usefulness, Satisfaction, and Ease of Use Questionnaire. The questions were rated on a 5-point Likert scale, ranging from 1 (fully disagree) to 5 (fully agree), to assess the face validity and content validity of this simulator.
Results: Participants reported a predominantly positive experience with the VR-ECC simulator, with 96% (n = 22) agreeing that the simulator was a useful way of training ECC scenarios. All participants found it easy to interact with the software (100%, n = 23), and 82% of students (n = 9) believed it helped them remember the steps involved with initiating ECC. Finally, (87% [n = 20]) of participants believed the image quality and depth perception were good.

Conclusions: Our next-generation simulator was valid for face and content constructs, and almost all participants found it to be a useful way of training for ECC scenarios. This simulator represents a first step toward truly blended digital learning and a new interactive, flexible, and innovative modality for perfusion training.

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Impact factor: 1.6 ; Q onbekend

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3. Predictors of target lesion failure after treatment of left main, bifurcation, or chronic total occlusion lesions with ultrathin-strut drug-eluting coronary stents in the ULTRA registry
de Filippo O, Bruno F, Pinxterhuis TH, Gąsior M, Perl L, Gaido L, Tuttolomondo D, Greco A, Verardi R, Lo Martire G, Iannaccone M, Leone A, Liccardo G, Caglioni S, González Ferreiro R, Rodinò G, Musumeci G, Patti G, Borzillo I, Tarantini G, Wańha W, Casella B, Ploumen EH, Pyka Ł, Kornowski R, Gagnor A, Piccolo R, Roubin SR, Capodanno D, Zocca P, Conrotto F, De Ferrari GM, von Birgelen C, D'Ascenzo F.

Background: Data about the long-term performance of new-generation ultrathin-strut drug-eluting stents (DES) in challenging coronary lesions, such as left main (LM), bifurcation, and chronic total occlusion (CTO) lesions are scant.
Methods: The international multicenter retrospective observational ULTRA study included consecutive patients treated from September 2016 to August 2021 with ultrathin-strut (<70 μm) DES in challenging de novo lesions. Primary endpoint was target lesion failure (TLF): composite of cardiac death, target-lesion revascularization (TLR), target-vessel myocardial infarction (TVMI), or definite stent thrombosis (ST). Secondary endpoints included all-cause death, acute myocardial infarction (AMI), target vessel revascularization, and TLF components. TLF predictors were assessed with Cox multivariable analysis.
Results: Of 1801 patients (age: 66.6 ± 11.2 years; male: 1410 [78.3%]), 170 (9.4%) experienced TLF during follow-up of 3.1 ± 1.4 years. In patients with LM, CTO, and bifurcation lesions, TLF rates were 13.5%, 9.9%, and 8.9%, respectively. Overall, 160 (8.9%) patients died (74 [4.1%] from cardiac causes). AMI and TVMI rates were 6.0% and 3.2%, respectively. ST occurred in 11 (1.1%) patients while 77 (4.3%) underwent TLR. Multivariable analysis identified the following predictors of TLF: age, STEMI with cardiogenic shock, impaired left ventricular ejection fraction, diabetes, and renal dysfunction. Among the procedural variables, total stent length increased TLF risk (HR: 1.01, 95% CI: 1-1.02 per mm increase), while intracoronary imaging reduced the risk substantially (HR: 0.35, 95% CI: 0.12-0.82).
Conclusions: Ultrathin-strut DES showed high efficacy and satisfactory safety, even in patients with challenging coronary lesions. Yet, despite using contemporary gold-standard DES, the association persisted between established patient- and procedure-related features of risk and impaired 3-year clinical outcome.

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Impact factor: 2.3 ; Q3

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4. Age-Related Effects of COVID-19 Pandemic on Mechanical Reperfusion and 30-Day Mortality for STEMI: Results of the ISACS-STEMI COVID-19 Registry
De Luca G, Algowhary M, Uguz B, Oliveira DC, Ganyukov V, Busljetik O, 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 V, Lee MK, Juzar DA, de Moura Joaquim R, Paladino R, Milicic D, Davlouros P, Bakraceski N, Zilio F, Donazzan L,

Kraaijeveld A, Galasso G, Arpad L, 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-Silberman S, Ordoñez S, Arat Özkan A, Scheller B, Lehitola H, Teles R, Mantis C, Antti Y, Brum Silveira JA, Zoni CR, Bessonov I, Uccello G, Kochiadakis G, Alexopulos D, Uribe CE, Kanakakis J, Faurie B, Gabrielli G, Gutierrez Barrios A, Bachini JP, Rocha A, Tam FCC, Rodriguez A, Lukito AA, Saint-Joy V, Pessah G, Tuccillo A, Ielasi A, Cortese G, Parodi G, Burgadha MA, Kedhi E, Lamelas P, Suryapranata H, Nardin M, Verdoia M.

Background: The constraints in the management of patients with ST-segment elevation myocardial infarction (STEMI) during the COVID-19 pandemic have been suggested to have severely impacted mortality levels. The aim of the current analysis is to evaluate the age-related effects of the COVID-19 pandemic on mechanical reperfusion and 30-day mortality for STEMI within the registry ISACS-STEMI COVID-19.
Methods: This retrospective multicenter registry was performed in high-volume PPCI centers on four continents and included STEMI patients undergoing PPCI in March-June 2019 and 2020. Patients were divided according to age (< or ≥75 years). The main outcomes were the incidence and timing of PPCI, (ischemia time longer than 12 h and door-to-balloon longer than 30 min), and in-hospital or 30-day mortality.
Results: We included 16,683 patients undergoing PPCI in 109 centers. In 2020, during the pandemic, there was a significant reduction in PPCI as compared to 2019 (IRR 0.843 (95%-CI: 0.825-0.861, $p < 0.0001$). We found a significant age-related reduction (7%, $p = 0.015$), with a larger effect on elderly than on younger patients. Furthermore, we observed significantly higher 30-day mortality during the pandemic period, especially among the elderly (13.6% vs. 17.9%, adjusted HR (95% CI) = 1.55 [1.24-1.93], $p < 0.001$) as compared to younger patients (4.8% vs. 5.7%; adjusted HR (95% CI) = 1.25 [1.05-1.49], $p = 0.013$), as a potential consequence of the significantly longer ischemia time observed during the pandemic.
Conclusions: The COVID-19 pandemic had a significant impact on the treatment of patients with STEMI, with a 16% reduction in PPCI procedures, with a larger reduction and a longer delay to treatment among elderly patients, which may have contributed to increase in-hospital and 30-day mortality during the pandemic.

Gepubliceerd: J Clin Med. 2023;12(6).
Impact factor: 3.9 ; Q2

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5. SARS-CoV-2 Positivity, Stent Thrombosis, and 30-day Mortality in STEMI Patients Undergoing Mechanical Reperfusion

De Luca G, Algowhary M, Uguz B, Oliveira DC, Ganyukov V, Zimbakov Z, Cercek M, Okkels Jensen L, Loh PH, Calmac L, Roura IFG, 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, Kang-Yin Lee M, Juzar DA, de Moura Joaquim R, De Simone C, Milicic D, Davlouros P, Bakraceski N, Zilio F, Donazzan L, Kraaijeveld A, Galasso G, Arpad L, 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, Lozano Martínez-Luengas I, Boccalatte M, Bosa Ojeda F, Arellano-Serrano C, Caiazzo G, Cirrincione G, Kao HL, Sanchis Forés J, Vignali L, Pereira H, Manzo-Silbermann S, Ordoñez S, Arat Özkan A, Scheller B, Lehtola H, Teles R, Mantis C, Antti Y, Brum Silveira JA, Bessonov I, Zoni R, 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, Bellemain-Appaix A, Pessah G, Cortese G, Parodi G, Burgadha MA, Kedhi E, Lamelas P, Suryapranata H, Nardin M, Verdoia M.

SARS-Cov-2 has been suggested to promote thrombotic complications and higher mortality. The aim of the present study was to evaluate the impact of SARS-CoV-2 positivity on in-hospital outcome and 30-day mortality in ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI) enrolled in the International Survey on Acute Coronary Syndromes ST-segment elevation Myocardial Infarction (ISACS-STEMI COVID-19 registry. The 109 SARS-CoV-2 positive patients were compared with 2005 SARS-CoV-2 negative patients. Positive patients were older (P = .002), less often active smokers (P = .002), and hypercholesterolemic (P = .006), they presented more often later than 12 h (P = .037), more often to the hub and were more often in cardiogenic shock (P = .02), or requiring rescue percutaneous coronary intervention after failed thrombolysis (P < .0001). Lower postprocedural Thrombolysis in Myocardial Infarction 3 flow (P = .029) and more thrombectomy (P = .046) were observed. SARS-CoV-2 was associated with a significantly higher in-hospital mortality (25.7 vs 7%, adjusted Odds Ratio (OR) [95% Confidence Interval] = 3.2 [1.71-5.99], P < .001) in-hospital definite in-stent thrombosis (6.4 vs 1.1%, adjusted Odds Ratio [95% CI] = 6.26 [2.41-16.25], P < .001) and 30-day mortality (34.4 vs 8.5%, adjusted Hazard Ratio [95% CI] = 2.16 [1.45-3.23], P < .001), confirming that SARS-CoV-2 positivity is associated with impaired reperfusion, with negative prognostic consequences.

Gepubliceerd: Angiology. 2023;74(10):987-96.
Impact factor: 2.8 ; Q3

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6. Gender Difference in the Effects of COVID-19 Pandemic on Mechanical Reperfusion and 30-Day Mortality for STEMI: Results of the ISACS-STEMI COVID-19 Registry

De Luca G, Manzo-Silberman S, Algowhary M, Uguz B, Oliveira DC, Ganyukov V, Busljetik O, Cercek M, Okkels L, Loh PH, Calmac L, Ferrer GRI, 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 V, Lee MK, Juzar DA, de Moura Joaquim R, Paladino R, Milicic D, Davlouros P, Bakraceski N, Zilio F, Donazzan L, Kraaijeveld A, Galasso G, Arpad L, 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, Ojeda FB, Arellano-Serrano C, Caiazzo G, Cirrincione G, Kao HL, Forés JS, Vignali L, Pereira H, Ordoñez S, Arat Özkan A, Scheller B, Lehtola H, Teles R, Mantis C, Antti Y, Brum Silveira JA, Zoni CR, Bessonov I, Uccello G, Kochiadakis G, Alexopulos D, Uribe CE, Kanakakis J, Faurie B, Gabrielli G, Barrios AG, Bachini JP, Rocha A, Tam FCC, Rodriguez A, Lukito AA, Saint-Joy V, Pessah G, Tuccillo A, Ielasi A, Cortese G, Parodi G, Bouraghda MA, Moura M, Kedhi E, Lamelas P, Suryapranata H, Nardin M, Verdoia M.

Background: Several reports have demonstrated the impact of the COVID-19 pandemic on the management and outcome of patients with ST-segment elevation myocardial infarction (STEMI). The aim of the current analysis is to investigate the potential gender difference in the effects of the COVID-19 pandemic on mechanical reperfusion and 30-day mortality for STEMI patients within the ISACS-STEMI COVID-19 Registry.
Methods: This retrospective multicenter registry was performed in high-volume primary percutaneous coronary intervention (PPCI) centers on four continents and included STEMI patients undergoing PPCIs in March-June 2019 and 2020. Patients were divided according to gender. The main outcomes were the incidence and timing of the PPCI, (ischemia time ≥ 12 h and door-to-balloon ≥ 30 min) and in-hospital or 30-day mortality.
Results: We included 16683 STEMI patients undergoing PPCIs in 109 centers. In 2020 during the pandemic, there was a significant reduction in PPCIs compared to 2019 (IRR 0.843 (95% CI: 0.825-0.861, $p < 0.0001$). We did not find a significant gender difference in the effects of the COVID-19 pandemic on the numbers of STEMI patients, which were similarly reduced from 2019 to 2020 in both groups, or in the mortality rates. Compared to prepandemia, 30-day mortality was significantly higher during the pandemic period among female (12.1% vs. 8.7%; adjusted HR [95% CI] = 1.66 [1.31-

2.11], $p < 0.001$) but not male patients (5.8% vs. 6.7%; adjusted HR [95% CI] = 1.14 [0.96-1.34], $p = 0.12$).
Conclusions: The COVID-19 pandemic had a significant impact on the treatment of patients with STEMI, with a 16% reduction in PPCI procedures similarly observed in both genders. Furthermore, we observed significantly increased in-hospital and 30-day mortality rates during the pandemic only among females. *Trial registration number: NCT 04412655.*

Gepubliceerd: J Clin Med. 2023;12(3).
Impact factor: 3.9 ; Q2

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7. Impact of Sex on Clinical Outcomes in Patients undergoing Complex Percutaneous Coronary Angioplasty (from the e-ULTIMASTER Study)
Doolub G, Tonino PAL, Kedev S, Monségu J, Paradies V, Austin D, Spanó F, Roffi M, Fröbert O, von Birgelen C, Buchanan L, Mamas MAP.

Female gender has been shown to be associated with worse clinical outcomes after percutaneous coronary intervention (PCI). However, the impact of gender on the clinical outcomes of complex PCI is still poorly understood. This study examined the differences in patient and coronary lesion characteristics and longer-term clinical outcomes in male and female patients who underwent complex PCI. This was a sub-analysis of the e-ULTIMASTER study, which was a large, multicontinental, prospective, observational study enrolling 37,198 patients who underwent PCI with the Ultimaster stent. Patients who underwent complex PCI were stratified by gender. The primary outcome was target lesion failure at 12 months, defined as the composite of cardiac death, target vessel-related myocardial infarction, and clinically driven target lesion revascularization at 12 months. A total of 13,623 patients underwent complex procedures, of which 35.7% were women. Women were twice as likely as men to be aged ≥80 years (17.6% vs 9%, p <0.0001) and had a higher prevalence of cardiovascular risk factors. Women had fewer lesions treated than men (1.5 ± 0.8 vs 1.6 ± 0.8, p <0.0001) and fewer stents implanted (2.0 ± 1.1 vs 2.1 ± 1.1, p <0.0001). There was no statistically significant difference in clinical outcomes at 12 months between women and men. Event rates were comparable in women and men for target lesion failure (4.7% vs 4.3%, p = 0.30), target vessel failure (5.1% vs 4.9%, p = 0.73), and cardiac death (1.8% vs 1.7%, p = 0.80).In conclusion, our findings suggest no significant differences in clinical outcomes between women and men who underwent complex PCI.

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Impact factor: 2.8 ; Q3

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8. Simulators and Simulations for Extracorporeal Membrane Oxygenation: An ECMO Scoping Review
Duinmeijer WC, Fresiello L, Swol J, Torrella P, Riera J, Obreja V, Puślecki M, Dąbrowski M, Arens J, Halfwerk FR.

High-volume extracorporeal membrane oxygenation (ECMO) centers generally have better outcomes than (new) low-volume ECMO centers, most likely achieved by a suitable exposure to ECMO cases. To achieve a higher level of training, simulation-based training (SBT) offers an additional option for education and extended clinical skills. SBT could also help to improve the interdisciplinary team interactions. However, the level of ECMO simulators and/or simulations (ECMO sims) techniques may vary in purpose. We present a structured and objective classification of ECMO sims based on the broad experience of users and the developer for the available ECMO sims as low-, mid-, or high-

fidelity. This classification is based on overall ECMO sim fidelity, established by taking the median of the definition-based fidelity, component fidelity, and customization fidelity as determined by expert opinion. According to this new classification, only low- and mid-fidelity ECMO sims are currently available. This comparison method may be used in the future for the description of new developments in ECMO sims, making it possible for ECMO sim designers, users, and researchers to compare accordingly, and ultimately improve ECMO patient outcomes.

Gepubliceerd: J Clin Med. 2023;12(5).
Impact factor: 3.9 ; Q2

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9. National indication document and aortic valve replacement landscape in the Netherlands
Eerdekens R, van Steenbergen G, El Farissi M, Demandt J, van 't Veer M, Daeter E, Timmers L, de Weger A, Medendorp N, Tonino P, Transcatheter Heart Valve Intervention Registry Committee, Cardiothoracic Surgery Registry Committee of the Netherlands Heart Registry: Stoel MG, Speekenbrink RGH.

Introduction: Based on European guidelines, transcatheter aortic valve implementation (TAVI) could be the therapy of choice in patients with severe aortic stenosis aged ≥ 75 years. In the Netherlands, there has been a debate between healthcare providers and the National Health Care Institute regarding reimbursement for TAVI, which resulted in an indication document that defines TAVI patients who are eligible for reimbursement. This document has been effective since 1 January 2021.
Methods: We extracted data from the Netherlands Heart Registry for patients who underwent biological surgical aortic valve replacement (SAVR) or TAVI in the Netherlands from 2018 through 2021. We compared baseline characteristics and variables from the indication document for the subsequent years and age groups. We also analysed the annual SAVR/TAVI ratio.
Results: The total number of patients treated with SAVR or TAVI was constant in 2018-2021. Baseline characteristics of patients treated with TAVI did not differ throughout the years. The SAVR/TAVI ratio shifted towards a higher percentage of TAVI from 2018 to 2019. From 2019 to 2020, the TAVI percentage was constant. Since the implementation of the indication document (in 2021), a change in the SAVR/TAVI ratio was not found either.
Conclusion: Since the implementation of the national indication document for AVR in 2021, no major effect was seen for the SAVR versus TAVI landscape in the Netherlands.

Gepubliceerd: Neth Heart J. 2023;31(12):473-8.
Impact factor: 2.0 ; Q3

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10. Long-term outcomes of patients with normal fractional flow reserve and thin-cap fibroatheroma
Fabris E, Berta B, Hommels T, Roleder T, Hermanides RS, Rivero F, von Birgelen C, Escaned J, Camaro C, Kennedy MW, Pereira B, Magro M, Nef H, Reith S, Roleder-Dylewska M, Gasior P, Malinowski KP, De Luca G, Garcia-Garcia HM, Granada JF, Wojakowski W, Kedhi E.

Background: The long-term prognostic implications of fractional flow reserve (FFR)-negative lesions hosting vulnerable plaques remain unsettled.
Aims: The aim of this study was to evaluate the association of non-ischaemic lesions hosting optical coherence tomography (OCT)-detected thin-cap fibroatheromas (TCFA) with first and recurrent cardiovascular events during follow-up up to 5 years in a diabetes mellitus (DM) patient population.
Methods: COMBINE OCT-FFR is a prospective, international, double-blind, natural history study. Patients with DM and with ≥1 FFR-negative lesion were classified into 2 groups based on the

presence or absence of ≥1 TCFA lesion. The primary endpoint (PE) is a composite of cardiac mortality, target vessel-related myocardial infarction (TV-MI), clinically driven target lesion revascularisation (TLR), or unstable angina (UA) requiring hospitalisation during follow-up up to 5 years.
Results: Among 390 DM patients (age 67.5±9 years; 37% female) with ≥1 FFR-negative lesion, 292 (74.9%) were TCFA-negative while 98 (25.1%) were TCFA-positive. The PE occurred more frequently in TCFA-positive than in TCFA-negative patients (21.4% vs 8.2%, hazard ratio [HR] 2.89, 95% confidence interval [CI]: 1.61-5.20; p<0.001; 6.42 vs 2.46 events per 100 patient-years, rate ratio [RR] 2.61, 95% CI: 1.38-4.90; p=0.002). Furthermore, when TV-MI, TLR, and UA were treated as recurrent components of the PE, TCFA-positive patients experienced a higher risk of recurrent events (HR 2.89, 95% CI; 1.74-4.80; p<0.001; 13.45 vs 2.87 events per 100 patient-years, RR 4.69, 95% CI: 2.86-7.83; p<0.001). A multivariable analysis identified the presence of TCFA as an independent predictor of the PE (HR 2.76, 95% CI: 1.53-4.97; p<0.001).
Conclusions: OCT-detected TCFA-positive lesions, although not ischaemia-generating, are associated with an increased risk of adverse events during long-term follow-up.

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Impact factor: 6.2 ; Q1

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11. Impact of a comprehensive cardiac rehabilitation programme versus coronary revascularisation in patients with stable angina pectoris: study protocol for the PRO-FIT randomised controlled trial
Heutinck JM, De Koning IA, Vromen T, Van Geuns RM, Thijssen DHJ, Kemps HMC, PRO-FIT Research Group: de Man FHAF.

Background: Currently, in the majority of patients with stable angina pectoris (SAP) treatment consists of optimal medical treatment, potentially followed by coronary angiography and subsequent coronary revascularisation if necessary". Recent work questioned the effectiveness of these invasive procedures in reducing re-events and improving prognosis. The potential of exercise-based cardiac rehabilitation on clinical outcomes in patients with coronary artery disease is well-known. However, in the modern era, no studies compared the effects of cardiac rehabilitation versus coronary revascularisation in patients with SAP.
Methods: In this multicentre randomised controlled trial, 216 patients with stable angina pectoris and residual anginal complaints under optimal medical treatment will be randomised to: 1) usual care (i.e., coronary revascularisation), or 2) a 12-month cardiac rehabilitation (CR) programme. CR consists of a multidisciplinary intervention, including education, exercise training, lifestyle coaching and a dietary intervention with a stepped decline in supervision. The primary outcome will be anginal complaints (Seattle Angina Questionnaire-7) following the 12-month intervention. Secondary outcomes include cost-effectiveness, ischemic threshold during exercise, cardiovascular events, exercise capacity, quality of life and psychosocial wellbeing.
Discussion: In this study, we will examine the hypothesis that multidisciplinary CR is at least equally effective in reducing anginal complaints as the contemporary invasive approach at 12-months follow-up for patients with SAP. If proven successful, this study will have significant impact on the treatment of patients with SAP as multidisciplinary CR is a less invasive and potentially less costly and better sustainable treatment than coronary revascularisations.
Trial registration: Netherlands Trial Register, NL9537. Registered 14 June 2021.

Gepubliceerd: BMC Cardiovasc Disord. 2023;23(1):238.
Impact factor: 2.1 ; Q3

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12. Sex differences in cardiovascular complications and mortality in hospital patients with covid-19: registry based observational study
Hockham C, Linschoten M, Asselbergs FW, Ghossein C, Woodward M, Peters SAE, CAPACITY-COVID Collaborative Consortium: Delsing CE, Meijs MFL.

Objective: To assess whether the risk of cardiovascular complications of covid-19 differ between the sexes and to determine whether any sex differences in risk are reduced in individuals with pre-existing cardiovascular disease.
Design: Registry based observational study.
Setting: 74 hospitals across 13 countries (eight European) participating in CAPACITY-COVID (Cardiac complicAtions in Patients With SARS Corona vIrus 2 regisTrY), from March 2020 to May 2021.
Participants: All adults (aged ≥18 years), predominantly European, admitted to hospital with highly suspected covid-19 disease or covid-19 disease confirmed by positive laboratory test results (n=11 167 patients).
Main outcome measures: Any cardiovascular complication during admission to hospital. Secondary outcomes were in-hospital mortality and individual cardiovascular complications with ≥20 events for each sex. Logistic regression was used to examine sex differences in the risk of cardiovascular outcomes, overall and grouped by pre-existing cardiovascular disease.
Results: Of 11 167 adults (median age 68 years, 40% female participants) included, 3423 (36% of whom were female participants) had pre-existing cardiovascular disease. In both sexes, the most common cardiovascular complications were supraventricular tachycardias (4% of female participants, 6% of male participants), pulmonary embolism (3% and 5%), and heart failure (decompensated or de novo) (2% in both sexes). After adjusting for age, ethnic group, pre-existing cardiovascular disease, and risk factors for cardiovascular disease, female individuals were less likely than male individuals to have a cardiovascular complication (odds ratio 0.72, 95% confidence interval 0.64 to 0.80) or die (0.65, 0.59 to 0.72). Differences between the sexes were not modified by pre-existing cardiovascular disease; for the primary outcome, the female-to-male ratio of the odds ratio in those without, compared with those with, pre-existing cardiovascular disease was 0.84 (0.67 to 1.07).
Conclusions: In patients admitted to hospital for covid-19, female participants were less likely than male participants to have a cardiovascular complication. The differences between the sexes could not be attributed to the lower prevalence of pre-existing cardiovascular disease in female individuals. The reasons for this advantage in female individuals requires further research.

Gepubliceerd: BMJ Med. 2023;2(1):e000245.
Impact factor: onbekend

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13. Impact of multisite artery disease on clinical outcomes after percutaneous coronary intervention: an analysis from the e-Ultimaster registry
Kobo O, Saada M, von Birgelen C, Tonino PAL, Íñiguez-Romo A, Fröbert O, Halabi M, Oemrawsingh RM, Polad J, AJJ IJ, Roffi M, Aminian A, Mamas MA, Roguin A.

Background: Multisite artery disease is considered a 'malignant' type of atherosclerotic disease associated with an increased cardiovascular risk, but the impact of multisite artery disease on clinical outcomes after percutaneous coronary intervention (PCI) is unknown.
Methods: Patients enrolled in the large, prospective e-Ultimaster study were grouped into (1) those without known prior vascular disease, (2) those with known single-territory vascular disease, and (3) those with known two to three territories (i.e coronary, cerebrovascular, or peripheral) vascular disease (multisite artery disease). The primary outcome was coronary target lesion failure (TLF), defined as the composite of cardiac death, target vessel-related myocardial infarction, and clinically driven target lesion revascularization at 1-year. Inverse propensity score weighted (IPSW) analysis was performed to address differences in baseline patient and lesion characteristics.

Results: Of the 37 198 patients included in the study, 62.3% had no prior known vascular disease, 32.6% had single-territory vascular disease, and 5.1% had multisite artery disease. Patients with known vascular disease were older and were more likely to be men and to have more co-morbidities. After IPSW, the TLF rate incrementally increased with the number of diseased vascular beds (3.16%, 4.44%, and 6.42% for no, single, and multisite artery disease, respectively, $P < 0.01$ for all comparisons). This was also true for all-cause death (2.22%, 3.28%, and 5.29%, $P < 0.01$ for all comparisons) and cardiac mortality (1.26%, 1.91%, and 3.62%, $P \leq 0.01$ for all comparisons).
Conclusions: Patients with previously known vascular disease experienced an increased risk of adverse cardiovascular events and mortality post-PCI. This risk is highest among patients with multisite artery disease.
Trial Registration: URL: https://www.clinicaltrials.gov. Unique identifier: NCT02188355.

Gepubliceerd: Eur Heart J Qual Care Clin Outcomes. 2023;9(4):417-26.
Impact factor: 5.2 ; Q2

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14. Variables associated with in-hospital and postdischarge outcomes after postcardiotomy extracorporeal membrane oxygenation: Netherlands Heart Registration Cohort
Mariani S, van Bussel BCT, Ravaux JM, Roefs MM, De Piero ME, Di Mauro M, Willers A, Segers P, Delnoij T, van der Horst ICC, Maessen J, Lorusso R, Netherlands Heart Registration Cardiothoracic Surgery Registration Committee: Speekenbrink RGH.

Objectives: Extracorporeal membrane oxygenation (ECMO) for postcardiotomy cardiogenic shock has been increasingly used without concomitant mortality reduction. This study aims to investigate determinants of in-hospital and postdischarge mortality in patients requiring postcardiotomy ECMO in the Netherlands.
Methods: The Netherlands Heart Registration collects nationwide prospective data from cardiac surgery units. Adults receiving intraoperative or postoperative ECMO included in the register from January 2013 to December 2019 were studied. Survival status was established through the national Personal Records Database. Multivariable logistic regression analyses were used to investigate determinants of in-hospital (3 models) and 12-month postdischarge mortality (4 models). Each model was developed to target specific time points during a patient's clinical course.
Results: Overall, 406 patients (67.2% men, median age, 66.0 years [interquartile range, 55.0-72.0 years]) were included. In-hospital mortality was 51.7%, with death occurring in a median of 5 days (interquartile range, 2-14 days) after surgery. Hospital survivors (n = 196) experienced considerable rates of pulmonary infections, respiratory failure, arrhythmias, and deep sternal wound infections during a hospitalization of median 29 days (interquartile range, 17-51 days). Older age (odds ratio [OR], 1.02; 95% CI, 1.0-1.04) and preoperative higher body mass index (OR, 1.08; 95% CI, 1.02-1.14) were associated with in-hospital death. Within 12 months after discharge, 35.1% of hospital survivors (n = 63) died. Postoperative renal failure (OR, 2.3; 95% CI, 1.6-4.9), respiratory failure (OR, 3.6; 95% CI, 1.3-9.9), and re-thoracotomy (OR, 2.9; 95% CI, 1.3-6.5) were associated with 12-month postdischarge mortality.
Conclusions: In-hospital and postdischarge mortality after postcardiotomy ECMO in adults remains high in the Netherlands. ECMO support in patients with higher age and body mass index, which drive associations with higher in-hospital mortality, should be carefully considered. Further observations suggest that prevention of re-thoracotomies, renal failure, and respiratory failure are targets that may improve postdischarge outcomes.

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Impact factor: 6.0 ; Q1

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15. Genetic Burden of TNNI3K in Diagnostic Testing of Patients With Dilated Cardiomyopathy and Supraventricular Arrhythmias
Pham C, Andrzejczyk K, Jurgens SJ, Lekanne Deprez R, Palm KCA, Vermeer AMC, Nijman J, Christiaans I, Barge-Schaapveld D, van Dessel P, Beekman L, Choi SH, Lubitz SA, Skoric-Milosavljevic D, van den Bersselaar L, Jansen PR, Copier JS, Ellinor PT, Wilde AAM, Bezzina CR, Lodder EM.

Background: Genetic variants in *TNNI3K* (troponin-I interacting kinase) have previously been associated with dilated cardiomyopathy (DCM), cardiac conduction disease, and supraventricular tachycardias. However, the link between *TNNI3K* variants and these cardiac phenotypes shows a lack of consensus concerning phenotype and protein function.
Methods: We describe a systematic retrospective study of a cohort of patients undergoing genetic testing for cardiac arrhythmias and cardiomyopathy including *TNNI3K*. We further performed burden testing of *TNNI3K* in the UK Biobank. For 2 novel *TNNI3K* variants, we tested cosegregation. TNNI3K kinase function was estimated by TNNI3K autophosphorylation assays.
Results: We demonstrate enrichment of rare coding *TNNI3K* variants in DCM patients in the Amsterdam cohort. In the UK Biobank, we observed an association between *TNNI3K* missense (but not loss-of-function) variants and DCM and atrial fibrillation. Furthermore, we demonstrate genetic segregation for 2 rare variants, TNNI3K-p.Ile512Thr and TNNI3K-p.His592Tyr, with phenotypes consisting of DCM, cardiac conduction disease, and supraventricular tachycardia, together with increased autophosphorylation. In contrast, TNNI3K-p.Arg556_Asn590del, a likely benign variant, demonstrated depleted autophosphorylation.
Conclusions: Our findings demonstrate an increased burden of rare coding *TNNI3K* variants in cardiac patients with DCM. Furthermore, we present 2 novel likely pathogenic *TNNI3K* variants with increased autophosphorylation, suggesting that enhanced autophosphorylation is likely to drive pathogenicity.

Gepubliceerd: Circ Genom Precis Med. 2023;16(4):328-36.
Impact factor: 7.4 ; Q1

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16. First myocardial infarction in patients with premature coronary artery disease: insights into patient characteristics and outcome after treatment with contemporary stents
Pinxterhuis TH, Ploumen EH, Doggen CJM, Hartmann M, Schotborgh CE, Anthonio RL, Roguin A, Danse PW, Benit E, Aminian A, Linssen GCM, von Birgelen C.

Aims: Patients with premature coronary artery disease (CAD) have a higher incidence of myocardial infarction (MI) than patients with non-premature CAD. The aim of the present study is to asess differences in clinical outcome after a first acute MI, percutaneously treated with new-generation drug-eluting stents between patients with premature and non-premature CAD.
Methods and results: We pooled and analysed the characteristics and clinical outcome of all patients with a first MI (and no previous coronary revascularization) at time of enrolment, in four large-scale drug-eluting stent trials. Coronary artery disease was classified premature in men aged <50 and women <55 years. Myocardial infarction patients with premature and non-premature CAD were compared. The main endpoint was major adverse cardiac events (MACE): all-cause mortality, any MI, emergent coronary artery bypass surgery, or clinically indicated target lesion revascularization. Of 3323 patients with a first MI, 582 (17.5%) had premature CAD. These patients had lower risk profiles and underwent less complex interventional procedures than patients with non-premature CAD. At 30-day follow-up, the rates of MACE [hazard ratio (HR): 0.22, 95% confidence interval (CI): 0.07-0.71; P = 0.005), MI (HR: 0.22, 95% CI: 0.05-0.89; P = 0.020), and target vessel failure (HR: 0.30, 95% CI: 0.11-0.82; P = 0.012) were lower in patients with premature CAD. At 1 year, premature CAD was independently associated with lower rates of MACE (adjusted HR: 0.50, 95% CI: 0.26-0.96; P = 0.037)

and all-cause mortality (adjusted HR: 0.24, 95% CI: 0.06-0.98; P = 0.046). At 2 years, premature CAD was independently associated with lower mortality (adjusted HR: 0.16, 95% CI: 0.05-0.50; P = 0.002). **Conclusions:** First MI patients with premature CAD, treated with contemporary stents, showed lower rates of MACE and all-cause mortality than patients with non-premature CAD, which is most likely related to differences in cardiovascular risk profile. TWENTE trials: TWENTE I, clinicaltrials.gov: NCT01066650), DUTCH PEERS (TWENTE II, NCT01331707), BIO-RESORT (TWENTE III, NCT01674803), and BIONYX (TWENTE IV, NCT02508714).

Gepubliceerd: Eur Heart J Acute Cardiovasc Care. 2023;12(11):774-81.
Impact factor: 4.1 ; Q2

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17. Impact of premature coronary artery disease on adverse event risk following first percutaneous coronary intervention
Pinxterhuis TH, Ploumen EH, Zocca P, Doggen CJM, Schotborgh CE, Anthonio RL, Roguin A, Danse PW, Benit E, Aminian A, Hartmann M, Linssen GCM, von Birgelen C.

Objectives: We assessed differences in risk profile and 3-year outcome between patients undergoing percutaneous coronary intervention (PCI) for *premature* and *non-premature* coronary artery disease (CAD).
Background: The prevalence of CAD increases with age, yet some individuals develop obstructive CAD at younger age.
Methods: Among participants in four randomized all-comers PCI trials, without previous coronary revascularization or myocardial infarction (MI), we compared patients with premature (men <50 years; women <55 years) and non-premature CAD. Various clinical endpoints were assessed, including multivariate analyses.
Results: Of 6,171 patients, 887 (14.4%) suffered from premature CAD. These patients had fewer risk factors than patients with non-premature CAD, but were more often smokers (60.7% vs. 26.4%) and overweight (76.2% vs. 69.8%). In addition, premature CAD patients presented more often with ST-segment elevation MI and underwent less often treatment of multiple vessels, and calcified or bifurcated lesions. Furthermore, premature CAD patients had a lower all-cause mortality risk (adj.HR: 0.23, 95%-CI: 0.10-0.52; $p < 0.001$), but target vessel revascularization (adj.HR: 1.63, 95%-CI: 1.18-2.26; $p = 0.003$) and definite stent thrombosis risks (adj.HR: 2.24, 95%-CI: 1.06-4.72; $p = 0.034$) were higher. MACE rates showed no statistically significant difference (6.6% vs. 9.4%; adj.HR: 0.86, 95%-CI: 0.65-1.16; $p = 0.33$).
Conclusions: About one out of seven PCI patients was treated for premature CAD. These patients had less complex risk profiles than patients with non-premature CAD; yet, their risk of repeated revascularization and stent thrombosis was higher. As lifetime event risk of patients with premature CAD is known to be particularly high, further efforts should be made to improve modifiable risk factors such as smoking and overweight.
Twente trials: (TWENTE I, clinicaltrials.gov: *NCT01066650*), DUTCH PEERS (TWENTE II, *NCT01331707*), BIO-RESORT (TWENTE III, *NCT01674803*), and BIONYX (TWENTE IV, *NCT02508714*).

Gepubliceerd: Front Cardiovasc Med. 2023;10:1160201.
Impact factor: 3.6 ; Q2

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18. Risk of bleeding after percutaneous coronary intervention and its impact on further adverse events in clinical trial participants with comorbid peripheral arterial disease
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: Both patients with obstructive coronary artery disease (CAD) and patients with peripheral arterial disease (PADs) have an increased bleeding risk. Information is scarce on bleeding in CAD patients, treated with percutaneous coronary intervention (PCI), who have comorbid PADs. We assessed whether PCI patients with PADs have a higher bleeding risk than PCI patients without PADs. Furthermore, in PCI patients with PADs we evaluated the extent by which bleeding increased the risk of further adverse events.
Methods: Three-year pooled patient-level data of two randomized PCI trials (BIO-RESORT, BIONYX) with drug-eluting stents were analyzed to assess mortality and the composite endpoint major adverse cardiac events (MACE: all-cause mortality, any myocardial infarction, emergent coronary artery bypass surgery, or target lesion revascularization).
Results: Among 5989 all-comer patients, followed for 3 years, bleeding occurred in 7.7% (34/440) with comorbid PADs and 5.0% (279/5549) without PADs (HR: 1.59, 95%CI: 1.11-2.23, p = 0.010). Of all PADs patients, those with a bleeding had significantly higher rates of all-cause mortality (HR: 4.70, 95%CI: 2.37-9.33, p < 0.001) and MACE (HR: 2.39, 95%CI: 1.23-4.31, p = 0.003). Furthermore, PADs patients with a bleeding were older (74.4 ± 6.9 vs. 67.4 ± 9.5, p < 0.001). After correction for age and other potential confounders, bleeding remained independently associated with all-cause mortality (adj.HR: 2.97, 95%CI: 1.37-6.43, p = 0.006) while the relation of bleeding with MACE became borderline non-significant (adj.HR: 1.85, 95%CI: 0.97-3.55, p = 0.06).
Conclusion: PCI patients with PADs had a higher bleeding risk than PCI patients without PADs. In PADs patients, bleeding was associated with all-cause mortality, even after adjustment for potential confounders.

Gepubliceerd: Int J Cardiol. 2023;374:27-32.
Impact factor: 3.5 ; Q2

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19. Outcome of percutaneous coronary intervention using ultrathin-strut biodegradable polymer sirolimus-eluting versus thin-strut durable polymer zotarolimus-eluting stents in patients with comorbid peripheral arterial disease: a post-hoc analysis from two randomized trials
Pinxterhuis TH, Ploumen EH, Zocca P, Doggen CJM, Schotborgh CE, Anthonio RL, Roguin A, Danse PW, Benit E, Aminian A, van Houwelingen KG, Linssen GCM, Geelkerken RH, von Birgelen C.

Background: In patients with peripheral arterial disease (PADs), who underwent percutaneous coronary intervention (PCI), little is known about the potential impact of using different new-generation drug-eluting stents (DES) on outcome. In PCI all-comers, the results of most between-stent comparisons-stratified by strut thickness-suggested some advantage of coronary stents with ultrathin-struts. The current post-hoc analysis aimed to assess outcomes of PCI with ultrathin-strut biodegradable polymer sirolimus-eluting stents (BP-SES) *vs.* thin-strut durable polymer zotarolimus-eluting stents (DP-ZES) in patients with PADs.
Methods: We pooled 3-year patient-level data from two large-scale randomized all-comer trials to compare Orsiro ultrathin-strut BP-SES *vs.* Resolute-type thin-strut DP-ZES in trial participants with concomitant PADs. BIO-RESORT (December 2012 to August 2015) and BIONYX (October 2015 to December 2016) included all-comer patients who were aged 18 years or older, capable of providing informed consent, and required a PCI. The trials had web-based randomization, with block sizes of 4 and 8, performed in a 1:1:1 or 1:1 fashion. Assessors, research staff, and patients were blinded to the type of stent used. We assessed the composite main clinical endpoint target vessel failure [TVF: cardiac death, target vessel related myocardial infarction (MI), or clinically indicated target vessel revascularization (TVR)], its components, and stent thrombosis.
Results: Of 4,830 trial participants, 360 had PADs: 177 (49.2%) were treated with BP-SES and 183 (50.8%) with DP-ZES. Baseline characteristics were similar. For BP-SES, the 3-year TVF rate was 11.0% and for DP-ZES 17.9% [hazard ratio (HR): 0.59, 95% CI: 0.33-1.04; P=0.07]. For BP-SES, the TVR rate

was lower than for DP-ZES (4.1% *vs.* 11.0%; HR: 0.36, 95% CI: 0.15-0.86; P=0.016), but this did not translate into between-group differences in cardiac death or MI. In small vessels (<2.75 mm), the TVR rate was also lower in BP-SES (5.6% *vs.* 13.9%; HR: 0.32, 95% CI: 0.11-0.91; P=0.024). Definite-or-probable stent thrombosis rates were 1.2% and 2.3% (P=0.43).
Conclusions: In PCI patients with PADs, the 3-year TVF incidence was numerically lower in the ultrathin-strut BP-SES *vs.* the thin-strut DP-ZES group. Furthermore, TVR risk was significantly lower in ultrathin-strut BP-SES, mainly driven by a lower TVR rate in small vessels.
Trial registration: BIO-RESORT trial: *clinicaltrials.gov* (*NCT01674803*); BIONYX trial: *clinicaltrials.gov* (*NCT02508714*).

Gepubliceerd: Cardiovasc Diagn Ther. 2023;13(4):673-85.
Impact factor: 2.4 ; Q3

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20. Morphological characteristics of lesions with thin cap fibroatheroma-a substudy from the COMBINE (OCT-FFR) trial
Roleder-Dylewska M, Gasior P, Hommels TM, Roleder T, Berta B, Ang HY, Ng JCK, Hermanides RS, Fabris E, AJJ IJ, Kauer F, Alfonso F, von Birgelen C, Escaned J, Camaro C, Kennedy MW, Pereira B, Magro M, Nef H, Reith S, Malinowski K, De Luca G, Garcia Garcia HM, Granada JF, Wojakowski W, Kedhi E.

Aims: To study if any qualitative or quantitative optical coherence tomography (OCT) variables in combination with thin cap fibroatheroma (TCFA) patients could improve the identification of lesions at risk for future major adverse cardiac events (MACEs).
Methods and results: From the 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: COMBINE (OCT-FFR) trial database (NCT02989740), we performed a detailed assessment OCT qualitative and quantitative variables in TCFA carrying diabetes mellitus (DM) patients with vs. without MACE during follow-up. MACEs were defined as a composite of cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization, and hospitalization for unstable angina. From the 390 fractional flow reserve (FFR)-negative DM patients, 98 (25.2%) had ≥1 OCT-detected TCFA, of which 13 (13.3%) had MACE and 85 (86.7%) were event-free (non-MACE). The baseline characteristics were similar between both groups; however, a smaller minimal lumen area (MLA) and lower mean FFR value were observed in MACE group (1.80 vs. 2.50 mm2, P = 0.01, and 0.85 vs. 0.89, P = 0.02, respectively). Prevalence of healed plaque (HP) was higher in the MACE group (53.85 vs. 21.18%, P = 0.01). TCFA were predominantly located proximal to the MLA. TCFA area was smaller in the MACE group, while no difference was observed regarding the lesion area.
Conclusion: Within TCFA carrying patients, a smaller MLA, lower FFR values, and TCFA location adjacent to a HP were associated with future MACE. Carpet-like measured lesion area surface was similar, while the TCFA area was smaller in the MACE arm, and predominantly located proximal to the MLA.

Gepubliceerd: Eur Heart J Cardiovasc Imaging. 2023;24(5):687-93.
Impact factor: 6.3 ; Q1

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21. Impact of chronic kidney disease and diabetes on clinical outcomes in women undergoing PCI
Spirito A, Itchhaporia D, Sartori S, Camenzind E, Chieffo A, Dangas GD, Galatius S, Jeger RV, Kandzari DE, Kastrati A, Kim HS, Kimura T, Leon MB, Mehta LS, Mikhail GW, Morice MC, Nicolas J, Pileggi B,

Serruys PW, Smits PC, Steg PG, Stone GW, Valgimigli M, Vogel B, von Birgelen C, Weisz G, Wijns W, Windecker S, Mehran R.

Background: For women undergoing drug-eluting stent (DES) implantation, the individual and combined impact of chronic kidney disease (CKD) and diabetes mellitus (DM) on outcomes is uncertain.
Aims: We sought to assess the impact of CKD and DM on prognosis in women after DES implantation.
Methods: We pooled patient-level data on women from 26 randomised controlled trials comparing stent types. Women receiving DES were stratified into 4 groups based on CKD (defined as creatine clearance <60 mL/min) and DM status. The primary outcome at 3 years after percutaneous coronary intervention was the composite of all-cause death or myocardial infarction (MI); secondary outcomes included cardiac death, stent thrombosis and target lesion revascularisation.
Results: Among 4,269 women, 1,822 (42.7%) had no CKD/DM, 978 (22.9%) had CKD alone, 981 (23.0%) had DM alone, and 488 (11.4%) had both conditions. The risk of all-cause death or MI was not increased in women with CKD alone (adjusted hazard ratio [adj. HR] 1.19, 95% confidence interval [CI]: 0.88-1.61) nor DM alone (adj. HR 1.27, 95% CI: 0.94-1.70), but was significantly higher in women with both conditions (adj. HR 2.64, 95% CI: 1.95-3.56; interaction p-value <0.001). CKD and DM in combination were associated with an increased risk of all secondary outcomes, whereas alone, each condition was only associated with all-cause death and cardiac death.
Conclusions: Among women receiving DES, the combined presence of CKD and DM was associated with a higher risk of the composite of death or MI and of any secondary outcome, whereas alone, each condition was associated with an increase in all-cause and cardiac death.

Gepubliceerd: EuroIntervention. 2023;19(6):493-501.
Impact factor: 6.2 ; Q1

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22. Hospital utilisation and the costs associated with complications of ICD implantation in a contemporary primary prevention cohort
van Barreveld M, Verstraelen TE, Buskens E, van Dessel P, Boersma LVA, Delnoy P, Tuinenburg AE, Theuns D, van der Voort PH, Kimman GP, Zwinderman AH, Wilde AAM, Dijkgraaf MGW.

Introduction: Implantation of an implantable cardioverter defibrillator (ICD) is standard care for primary prevention of sudden cardiac death. However, ICD-related complications are increasing as the population of ICD recipients grows.
Methods: ICD-related complications in a national DO-IT Registry cohort of 1442 primary prevention ICD patients were assessed in terms of additional use of hospital care resources and costs.
Results: During a median follow-up of 28.7 months (IQR 25.2-33.7) one or more complications occurred in 13.5% of patients. A complication resulted in a surgical intervention in 53% of cases and required on average 3.65 additional hospital days. The additional hospital costs were €6,876 per complication or €8,110 per patient, to which clinical re-interventions and additional hospital days contributed most. Per category of complications, infections required most hospital utilisation and were most expensive at an average of €22,892. The mean costs were €5,800 for lead-related complications, €2,291 for pocket-related complications and €5,619 for complications due to other causes. We estimate that the total yearly incidence-based costs in the Netherlands for hospital management of ICD-related complications following ICD implantation for primary prevention are €2.7 million.
Conclusion: Complications following ICD implantation are related to a substantial additional need for hospital resources. When performing cost-effectiveness analyses of ICD implantation, including the costs associated with complications, one should be aware that real-world complication rates may deviate from trial data. Considering the economic implications, strategies to reduce the incidence of complications are encouraged.

Gepubliceerd: Neth Heart J. 2023;31(6):244-53.
Impact factor: 2.0 ; Q3

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23. Conservative versus Invasive Strategy in Elderly Patients with Non-ST-Elevation Myocardial Infarction: Insights from the International POPular Age Registry
van den Broek WWA, Gimbel ME, Chan Pin Yin D, Azzahhafi J, Hermanides RS, Runnett C, Storey RF, Austin D, Oemrawsingh R, Cooke J, Galasko G, Walhout RJ, Schellings D, Brinckman SL, The HK, Stoel MG, Heestermans A, Nicastia D, Emans ME, van 't Hof AWJ, Alber H, Gerber R, van Bergen P, Aksoy I, Nasser A, Knaapen P, Botman CJ, Liem A, Kelder JC, Ten Berg JM.

This registry assessed the impact of conservative and invasive strategies on major adverse clinical events (MACE) in elderly patients with non-ST-elevation myocardial infarction (NSTEMI). Patients aged ≥75 years with NSTEMI were prospectively registered from European centers and followed up for one year. Outcomes were compared between conservative and invasive groups in the overall population and a propensity score-matched (PSM) cohort. MACE included cardiovascular death, acute coronary syndrome, and stroke. The study included 1190 patients (median age 80 years, 43% female). CAG was performed in 67% (N = 798), with two-thirds undergoing revascularization. Conservatively treated patients had higher baseline risk. After propensity score matching, 319 patient pairs were successfully matched. MACE occurred more frequently in the conservative group (total population 20% vs. 12%, (adj)HR 0.53, 95% CI 0.37-0.77, p = 0.001), remaining significant in the PSM cohort (18% vs. 12%, (adj)HR 0.50, 95% CI 0.31-0.81, p = 0.004). In conclusion, an early invasive strategy was associated with benefits over conservative management in elderly patients with NSTEMI. Risk factors associated with ischemia and bleeding should guide strategy selection rather than solely relying on age.

Gepubliceerd: J Clin Med. 2023;12(17).
Impact factor: 3.9 ; Q2

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24. Atrial fibrillation detected with outpatient cardiac rhythm monitoring in patients with ischemic stroke or TIA of undetermined cause
van der Maten G, Meijs MFL, van der Palen J, Brouwers P, von Birgelen C, van Opstal J, den Hertog HM.

Objectives: Guidelines advise cardiac rhythm monitoring for 3 up to 30 days for detecting atrial fibrillation (AF) in patients with ischemic stroke of undetermined cause. However, the optimal monitoring duration is unknown. We aimed to determine the AF detection rate during 7-day outpatient cardiac rhythm monitoring in this patient group.
Methods: Participants from a large tertiary hospital in a prospective observational study (ATTEST) underwent outpatient cardiac rhythm monitoring after a negative standard diagnostic evaluation (i.e., 12-lead electrocardiogram and in-hospital telemetry). Primary outcome was the rate of newly detected AF.
Results: We examined 373 patients [age: 67.8±11.6 years; women: 166(44.5%); stroke: 278(74.5%)]. Median monitoring duration was 7 days (Inter Quartile Range (IQR) 7-7), performed after median of 36 days (IQR 27-47). AF was newly detected in 17(4.6%) patients, 5.4% of patients with ischemic stroke and 2.1% of patients with TIA. 53% of AF was detected on day-1, after day-3 73% of new AF was found. First AF episodes were detected up to day-7. Diabetes and increasing age were independent predictors of new AF.

Conclusion: After ischemic stroke or TIA of undetermined cause, 7-day outpatient cardiac rhythm monitoring detected new AF in 4.6%. Patients with AF had significantly more cardiovascular risk factors. Although about 50% of first AF episodes occurred during the first day of monitoring, new AF was detected up to day-7, implying that the recommended minimum of 3 days cardiac rhythm monitoring after ischemic stroke of undetermined cause is insufficient. Subsequent long-term rhythm monitoring should be considered in selected patients.

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Impact factor: 2.5 ; Q3

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25. The genetic basis of apparently idiopathic ventricular fibrillation: a retrospective overview
Verheul LM, van der Ree MH, Groeneveld SA, Mulder BA, Christiaans I, Kapel GFL, Alings M, Bootsma M, Barge-Schaapveld D, Balt JC, Yap SC, Krapels IPC, Ter Bekke RMA, Volders PGA, van der Crabben SN, Postema PG, Wilde AAM, Dooijes D, Baas AF, Hassink RJ.

Aims: During the diagnostic work-up of patients with idiopathic ventricular fibrillation (VF), next-generation sequencing panels can be considered to identify genotypes associated with arrhythmias. However, consensus for gene panel testing is still lacking, and variants of uncertain significance (VUS) are often identified. The aim of this study was to evaluate genetic testing and its results in idiopathic VF patients.
Methods and results: We investigated 419 patients with available medical records from the Dutch Idiopathic VF Registry. Genetic testing was performed in 379 (91%) patients [median age at event 39 years (27-51), 60% male]. Single-gene testing was performed in 87 patients (23%) and was initiated more often in patients with idiopathic VF before 2010. Panel testing was performed in 292 patients (77%). The majority of causal (likely) pathogenic variants (LP/P, n = 56, 15%) entailed the DPP6 risk haplotype (n = 39, 70%). Moreover, 10 LP/P variants were found in cardiomyopathy genes (FLNC, MYL2, MYH7, PLN (two), TTN (four), RBM20), and 7 LP/P variants were identified in genes associated with cardiac arrhythmias (KCNQ1, SCN5A (2), RYR2 (four)). For eight patients (2%), identification of an LP/P variant resulted in a change of diagnosis. In 113 patients (30%), a VUS was identified. Broad panel testing resulted in a higher incidence of VUS in comparison to single-gene testing (38% vs. 3%, $P < 0.001$).
Conclusion: Almost all patients from the registry underwent, albeit not broad, genetic testing. The genetic yield of causal LP/P variants in idiopathic VF patients is 5%, increasing to 15% when including DPP6. In specific cases, the LP/P variant is the underlying diagnosis. A gene panel specifically for idiopathic VF patients is proposed.

Gepubliceerd: Europace. 2023;25(11).
Impact factor: 6.1 ; Q1

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26. Defining low- and high fidelity simulation in systematic reviews: The case of heart auscultation simulators
Halfwerk FR, Duinmeijer WC, Haumann R & Arens J.

Gepubliceerd: International Journal of Healthcare Simulation 2023, p1-2.
Impact factor: onbekend

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27. Sex-stratified patterns of emergency cardiovascular admissions prior and during the COVID-19 pandemic

Gajewski P, Błaziak M, Urban S, Garus M, Braunschweig F, Caldeira D, Gawor A, Greenwood JP, Guzik M, Halfwerk FR, Iwanek G, Jarocki M, Jura M, Krzystek-Korpacka M, Lewandowski, Ł, Lund LH, Matysiak M, Pinto F, Sleziak J, Wietrzyk W, Sokolski M, Biegus J, Ponikowski P, Zymliński R.

The COVID-19 pandemic has had a significant impact on global public health, with long-term consequences that are still largely unknown. This study aimed to assess the data regarding acute cardiovascular hospital admissions in five European centers before and during the pandemic. A multicenter, multinational observational registry was created, comparing admissions to the emergency departments during a 3-months period in 2020 (during the pandemic) with the corresponding period in 2019 (pre-pandemic). Data on patient demographics, COVID-19 test results, primary diagnosis, comorbidities, heart failure profile, medication use, and laboratory results were collected. A total of 8778 patients were included in the analysis, with 4447 patients in 2019 and 4331 patients in 2020. The results showed significant differences in the distribution of cardiovascular diseases between the two years. The frequency of pulmonary embolism (PE) increased in 2020 compared to 2019, while acute heart failure (AHF) and other cardiovascular diseases decreased. The odds of PE incidence among hospitalized patients in 2020 were 1.316-fold greater than in 2019. The incidence of AHF was 50.83% less likely to be observed in 2020, and the odds for other cardiovascular diseases increased by 17.42% between the 2 years. Regarding acute coronary syndrome (ACS), the distribution of its types differed between 2019 and 2020, with an increase in the odds of ST-segment elevation myocardial infarction (STEMI) in 2020. Stratification based on sex revealed further insights. Among men, the incidence of AHF decreased in 2020, while other cardiovascular diseases increased. In women, only the incidence of STEMI showed a significant increase. When analyzing the influence of SARS-CoV-2 infection, COVID-positive patients had a higher incidence of PE compared to COVID-negative patients. COVID-positive patients with ACS also exhibited symptoms of heart failure more frequently than COVID-negative patients. These findings provide valuable information on the impact of the COVID-19 pandemic on acute cardiovascular hospital admissions. The increased incidence of PE and changes in the distribution of other cardiovascular diseases highlight the importance of monitoring and managing cardiovascular health during and post pandemic period. The differences observed between sexes emphasize the need for further research to understand potential sex-specific effects of COVID-19 on cardiovascular outcomes.

Gepubliceerd: Sci Rep 2023;13(1):17924.
Impact factor: 3.8 ; Q1

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28. Effect of hollow fiber configuration and replacement on the gas exchange performance of artificial membrane lungs
Costa AM, Halfwerk FR, Thiel JN, Wiegmann B, Neidlin M, Arens J.

rtificial membrane lungs are composed of hollow fiber membranes. Blood flows with low velocities in the membrane bundle, forming a laminar boundary layer near the membrane surfaces that limits gas transfer. Passive blood mixing within the fiber array is utilized to overcome this limitation. Nevertheless, it is unclear to which extent blood mixing and fiber configuration contribute to the performance of membrane oxygenators.
This study aims to evaluate the effect of fiber configuration and replacement on the gas exchange performance of membrane oxygenators to contribute to a better understanding of the influence of blood mixing to gas transfer and the mechanisms of gas exchange in blood. Furthermore, designs in which hollow fibers of different functions could be combined in highly integrated membrane lungs are provided.
We analyzed the gas transfer performance of membrane oxygenators in a perpendicular configuration with 100%, 75%, or 50% of fibers open, and in a crossed configuration with 100% or 67% of fibers open. 95%–100% of the oxygen transfer of a fully open oxygenator could be maintained

in our prototypes with 25% of gas exchange fibers closed in a perpendicular configuration, indicating that several fibers contributed to gas exchange by mixing the blood flow. Closing fibers in a perpendicular configuration resulted in a lower decrease in oxygen transfer. This study contributes to the development of novel membrane oxygenators integrating fibers of different functionalities (e.g. oxygenation and dialysis) maintaining high gas exchange efficiency.

Gepubliceerd: J Membrane Sci 2023:680;121742.
Impact factor: onbekend

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29. A mobilization poster stimulates early in-hospital rehabilitation after cardiac surgery: a prospective sequential-group study
Halfwerk FR, Wielens N, Hulskotte S, Brusse-Keizer M, Grandjean JG.

Background: Patients infrequently mobilize at the surgical ward after cardiac surgery. Inactivity results in prolonged hospital stay, readmissions and increased cardiovascular mortality. Next, the course of in-hospital mobilization activities for patients is unclear. The aim was to evaluate early mobilization after heart surgery with a mobilization poster on the Activity Classification Guide for Inpatient Activities score from the American College for Sports Medicine (ACSM). Second, to develop a Thorax Centrum Twente (TCT) score to assess distinctive activities performed.
Methods: A poster was developed for the Moving is Improving! study to stimulate hospital mobilization after heart surgery. In this sequential-group study at a cardiothoracic surgery ward, 32 patients were included in the usual care group and 209 patients in the poster mobilization group. Change of ACSM and TCT scores over time were both defined as primary endpoints. Secondary endpoints included length of stay and survival. A subgroup analysis for coronary artery bypass grafting (CABG) was performed.
Results: ACSM score increased during hospital stay ($p < 0.001$). No significant increase of ACSM score was observed with a mobilization poster ($p = 0.27$), nor in the CABG subgroup ($p = 0.15$). The poster increased mobility to chair, toilet, corridor (all $p < 0.01$) and cycle ergometer ($p = 0.02$) as measured by the activity-specific TCT scores, without differences in length of stay or survival.
Conclusions: ACSM score measured day-to-day functional changes, without significant differences between the poster mobilization and usual care group. Actual activities measured with the TCT score did improve. The mobilization poster is now new standard care, and effects in other centers and other departments should be assessed.
Trial registration: This study does not fall under the ICMJE trial definition and was not registered.

Gepubliceerd: J Cardiothorac Surg. 2023;18(1):83.
Impact factor: 1.6 ; Q3

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30. Helical Propulsion in Low-Re Numbers with Near-Zero Angle of Attack
Ligtenberg LJW, Ekkelkamp IAA, Halfwerk FR, Goulas C, Arens J, Warlé M, Khalil I.

One approach to the wireless actuation and gravity compensation of untethered helical magnetic devices (UHMD) is through swimming with a non-zero angle of attack (AoA). This configuration allows us to counteract gravity, so that for a given desired path, we can move the UHMD controllably without drifting downward under its own weight. This study seeks to investigate the use a reduced-order model of the complex 6-degrees-of-freedom model of UHMDs in low Reynolds-number regime. A one-dimensional model representing the relative position of the UHMD with respect to an actuator rotating permanent magnet is used to predict a gap which yields bounded behavior of the open-loop system. Using geometric representation of the reduced-order model, the local bounded behavior of

the UHMD with near-zero AoA is attributed to periodic active magnetic suspension, which dominates near-zero AoA. Our numerical results are verified experimentally and bounded behavior of the UHMD demonstrates the capability to swim with near-zero AoA (6.3° ± 2.2°) without drifting downward. With this actuation strategy, it is unlikely that the orientation of the UHMD will be needed during noninvasive localization, making the control system dependent on only its position with respect to a prescribed trajectory. This strategy will also provide a computational advantage in adjusting the gap between the UHMD and a robotically controlled rotating permanent magnet actuator.

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Impact factor: onbekend

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31. Career perspectives for young cardiologists in the Netherlands: an update
Bosch L, Minneboo M, Baggen VJM, Beusekamp JC, Yilmaz D, Haroun D, Vorselaars VMM, Meijers WC.

Gepubliceerd: Neth Heart J 2023;31(11):454-455.
Impact factor: 1.7 ; Q3

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32. Changes in colloid oncotic pressure during cardiac surgery with different prime fluid strategies
Beukers AM, de Villiers Hugo J, Haumann RG, Boltje JWT, Khiam Ie EL, Loer SA, Bulte CSE, Vonk A.

Objective: In cardiac surgery, colloid oncotic pressure (COP) is affected by haemodilution that results from composition and volume of prime fluid of cardiopulmonary bypass (CPB). However, the extent to which different priming strategies alter COP is largely unknown. Therefore, we investigated the effect of different priming strategies on COP in on-pump cardiac surgery.
Methods: Patients (*n* = 60) were divided into 3 groups (*n* = 20 each), based on the center in which they were operated and the specific prime fluid strategy used in that center during the inclusion period. CPB prime fluids were either gelofusine-, albumin-, or crystalloid based, the latter two with or without retrograde autologous priming.
Results: In all groups, COP was lowest after weaning from CPB and one hour after CPB. Between groups, COP was lowest with gelofusine prime fluid (16.4, 16.8 mmHg, respectively) compared with crystalloids (MD: -1.9; 95% CI:-3.6, -0.2; *p* = .02 and MD: -2.4, 95% CI: -4.2, -0.7; *p* = .002) and albumin (MD: -1.8, 95% CI: -3.5, -0.50; *p* = .041 and MD: -2.4, 95% CI: -4.1, -0.7; *p* = .002). In all groups, the decrease in COP one hour after bypass compared to baseline correlated positively with fluid balance at the end of surgery (*p* < .001).
Conclusions: COP significantly decrease during CPB surgery with the largest decrease in COP at the end of surgery, while at the same time fluid balance increases. We suggest that prime fluid strategy should be carefully selected when maintenance of COP during cardiac surgery is desirable.

Gepubliceerd Perfusion 2023: 2676591231193626
Impact factor: 1.1 ; Q4

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33. Drug-eluting stents for ST-segment elevation myocardial infarction: extending the biodegradable versus durable polymer debate
Buiten RA, Ploumen EH.

Gepubliceerd: Lancet 2023;402(10416):1942-1943.

Impact factor: 98.4 ; Q1

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34. Remote haemodynamic monitoring of pulmonary artery pressures in patients with chronic heart failure (MONITOR-HF): a randomised clinical trial
Brugts JJ, Radhoe SP, Clephas, PRD, Aydin D, van Gent MWF, Szymanski MK, Rienstra M, van den Heuvel MH, da Fonseca CA, Linssen GCM, Borleffs CJW, Boersma E, Asselbergs FW, Mosterd A, Brunner-La Rocca HP, de Boer RA.

Background: The effect of haemodynamic monitoring of pulmonary artery pressure has predominantly been studied in the USA. There is a clear need for randomised trial data from patients treated with contemporary guideline-directed-medical-therapy with long-term follow-up in a different health-care system.
Methods: MONITOR-HF was an open-label, randomised trial, done in 25 centres in the Netherlands. Eligible patients had chronic heart failure of New York Heart Association class III and a previous heart failure hospitalisation, irrespective of ejection fraction. Patients were randomly assigned (1:1) to haemodynamic monitoring (CardioMEMS-HF system, Abbott Laboratories, Abbott Park, IL, USA) or standard care. All patients were scheduled to be seen by their clinician at 3 months and 6 months, and every 6 months thereafter, up to 48 months. The primary endpoint was the mean difference in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score at 12 months. All analyses were by intention-to-treat. This trial was prospectively registered under the clinical trial registration number NTR7673 (NL7430) on the International Clinical Trials Registry Platform.
Findings: Between April 1, 2019, and Jan 14, 2022, we randomly assigned 348 patients to either the CardioMEMS-HF group (n=176 [51%]) or the control group (n=172 [49%]). The median age was 69 years (IQR 61-75) and median ejection fraction was 30% (23-40). The difference in mean change in KCCQ overall summary score at 12 months was 7·13 (95% CI 1·51-12·75; p=0·013) between groups (+7·05 in the CardioMEMS group, p=0·0014, and -0·08 in the standard care group, p=0·97). In the responder analysis, the odds ratio (OR) of an improvement of at least 5 points in KCCQ overall summary score was OR 1·69 (95% CI 1·01-2·83; p=0·046) and the OR of a deterioration of at least 5 points was 0·45 (0·26-0·77; p=0·0035) in the CardioMEMS-HF group compared with in the standard care group. The freedom of device-related or system-related complications and sensor failure were 97·7% and 98·8%, respectively.
Interpretation: Haemodynamic monitoring substantially improved quality of life and reduced heart failure hospitalisations in patients with moderate-to-severe heart failure treated according to contemporary guidelines. These findings contribute to the aggregate evidence for this technology and might have implications for guideline recommendations and implementation of remote pulmonary artery pressure monitoring.
Funding: The Dutch Ministry of Health, Health Care Institute (Zorginstituut), and Abbott Laboratories.

Gepubliceerd: Lancet 2023;401(10394):2113-2123.
Impact factor: 98.4 ; Q1

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35. Exploring Patterns of COPD Exacerbations and Comorbid Flare-Ups
van Dijk SHB, Brusse-Keizer MGJ, Effing T, van der Valk P, Ploumen EH, van der Palen J, Doggen CJM, Lenferink A.

Background: Comorbidities are known to complicate disease management in patients with Chronic Obstructive Pulmonary Disease (COPD). This is partly due to lack of insight into the interplay of acute exacerbations of COPD (AECOPD) and comorbid flare-ups. This study aimed to explore patterns of AECOPDs and comorbid flare-ups.

Methods: Data of increased symptoms were extracted from a 12-month daily symptom follow-up database including patients with COPD and comorbidities (chronic heart failure (CHF), anxiety, depression) and transformed to visualizations of AECOPDs and comorbid flare-up patterns over time. Patterns were subsequently categorized using an inductive approach, based on both predominance (ie, which occurs most often) of AECOPDs or comorbid flare-ups, and their simultaneous (ie, simultaneous start in ≥ 50%) occurrence.
Results: We included 48 COPD patients (68 ± 9 years; comorbid CHF: 52%, anxiety: 40%, depression: 38%). In 25 patients with AECOPDs and CHF flare-ups, the following patterns were identified: AECOPDs predominant (n = 14), CHF flare-ups predominant (n = 5), AECOPDs nor CHF flare-ups predominant (n = 6). Of the 24 patients with AECOPDs and anxiety and/or depression flare-ups, anxiety and depression flare-ups occurred simultaneously in 15 patients. In 9 of these 24 patients, anxiety or depression flare-ups were observed independently from each other. In 31 of the included 48 patients, AECOPDs and comorbid flare-ups occurred mostly simultaneously.
Conclusion: Patients with COPD and common comorbidities show a variety of patterns of AECOPDs and comorbid flare-ups. Some patients, however, show repetitive patterns that could potentially be used to improve personalized disease management, if recognized.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis. 2023;18:2633-44.
Impact factor: 2.8 ; Q3

Totale impact factor: 298.5
Gemiddelde impact factor: 8.5

Aantal artikelen 1^{e}, 2^{e} of laatste auteur: 10
Totale impact factor: 120.0
Gemiddelde impact factor: 12.0

Waardegedreven zorg

1. Impact of immunosuppressive treatment and type of SARS-CoV-2 vaccine on antibody levels after three vaccinations in patients with chronic kidney disease or kidney replacement therapy
Bouwmans P, Messchendorp AL, Imhof C, Sanders JF, Hilbrands LB, Reinders MEJ, Vart P, Bemelman FJ, Abrahams AC, van den Dorpel RMA, Ten Dam M, de Vries APJ, Rispens T, Steenhuis M, Gansevoort RT, Hemmelder MH, RECOVAC Collaborators: Zwerink M, Brinkman JN.

Background: Patients with chronic kidney disease (CKD) or kidney replacement therapy demonstrate lower antibody levels after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination compared with healthy controls. In a prospective cohort, we analysed the impact of immunosuppressive treatment and type of vaccine on antibody levels after three SARS-CoV-2 vaccinations.
Methods: Control subjects (n = 186), patients with CKD G4/5 (n = 400), dialysis patients (n = 480) and kidney transplant recipients (KTR) (n = 2468) were vaccinated with either mRNA-1273 (Moderna), BNT162b2 (Pfizer-BioNTech) or AZD1222 (Oxford/AstraZeneca) in the Dutch SARS-CoV-2 vaccination programme. Third vaccination data were available in a subgroup of patients (n = 1829). Blood samples and questionnaires were obtained 1 month after the second and third vaccination. Primary endpoint was the antibody level in relation to immunosuppressive treatment and type of vaccine. Secondary endpoint was occurrence of adverse events after vaccination.
Results: Antibody levels after two and three vaccinations were lower in patients with CKD G4/5 and dialysis patients with immunosuppressive treatment compared with patients without immunosuppressive treatment. After two vaccinations, we observed lower antibody levels in KTR using mycophenolate mofetil (MMF) compared with KTR not using MMF [20 binding antibody unit (BAU)/mL (3-113) vs 340 BAU/mL (50-1492), P < .001]. Seroconversion was observed in 35% of KTR using MMF, compared with 75% of KTR not using MMF. Of the KTR who used MMF and did not seroconvert, eventually 46% seroconverted after a third vaccination. mRNA-1273 induces higher antibody levels as well as a higher frequency of adverse events compared with BNT162b2 in all patient groups.
Conclusions: Immunosuppressive treatment adversely affects the antibody levels after SARS-CoV-2 vaccination in patients with CKD G4/5, dialysis patients and KTR. mRNA-1273 vaccine induces a higher antibody level and higher frequency of adverse events.

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