Wetenschappelijk onderzoek in Medisch Spectrum Twente

2019

Inhoudsopgave

Voorwoord

Voor u ligt de 11e editie van het jaarlijkse overzicht van de wetenschappelijke output van medewerkers van Medisch Spectrum Twente. Het betreft het jaar 2019. Dit jaaroverzicht wordt ook buiten MST verspreid onder huisartsen, apothekers, fysiotherapeuten en andere wetenschappelijke instellingen in de regio.

De publicaties zijn gegroepeerd op vakgroep of maatschap. Niet op volgorde van belangrijkheid maar alfabetisch. Hierbij is als criterium genomen dat de publicatie terug te vinden moet zijn op PubMed en de publicatiedatum moet ook in 2019 zijn. De zogenaamde “Epub Ahead of Print” artikelen komen in de volgende uitgave. Daarnaast worden ook peer-reviewed artikelen uit Nederlandstalige tijdschriften opgenomen.

In 2019 zijn 232 unieke publicaties verschenen in peer-reviewed tijdschriften. Dit is vergelijkbare met voorgaande jaren. De gemiddelde impact score van alle artikelen is 6,12. Dit is het hoogste ooit! Dit jaar hebben we 4 keer in het absolute toptijdschrift New England Journal of Medicine gestaan, 2 keer in de Lancet en 4 keer in een subtijdschrift van de Lancet en ook nog een keer in de British Medical Journal.

Daarnaast wordt net als vorig jaar per publicatie ook weergegeven in welk kwartiel het tijdschrift staat in de betreffende categorie. Indien meerdere categoriën van toepassing zijn wordt het hoogste kwartiel genomen. We publiceerden in 52% in Q1, 29% in Q2, 15% in Q3 en 4% in Q4.
Qua promoties was 2019 een prima jaar met 9 promoties in MST.

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 2019 naast die van eerdere jaren weergegeven.

Ik wens u veel leesplezier toe,

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

	2011	2012	2013	2014	2015	2016	2017	2018	2019
Unieke publicaties	190	213	191	212	245	226	216	240	232
Impact factor	3,63	3,97	4,38	4,03	5,06	4,70	4,47	5,64	6.12

2016			2017			2018			2019		
Top 3: Aantal publicaties:											
1	Neurologie	41	1	Cardiologie	31	1	Cardiologie	40	1	Heelkunde	39
2	Cardiologie	39	2	Heelkunde	30	2	Neurologie	30	2	Neurologie	33
3	Med. School	33	3	Neurologie	28	3	Longziekten	28	3	Cardiologie	27
Top 3: Totale impact factor score:											
1	Cardiologie	251	1	Cardiologie	181	1	Cardiologie	306	1	Cardiologie	397
2	Neurologie	170	2	Neurologie	136	2	Intensive care	197	2	Heelkunde	216
3	Med. School	135	3	Heelkunde	116	3	Longziekten	148	3	Neurologie	197
Top 3: Gemiddelde impact factor score:											
1	Gynaecologie	16.7	1	Klin. Chemie	6.9	1	MDL	16.6	1	Cardiologie	14.7
2	Radiotherapie	8.2	2	Radiotherapie	6.7	2	Intensive care	14.2	2	Intensive care	12.4
3	Klin. chemie	6.9	3	Interne gnkd	6.1	3	Cardiologie	7.7	3	Klin. Farmacie	7.4
Top 3: Aantal publicaties als 1e, 2e of laatste auteur:											
1	Cardiologie	18	1	Cardiologie	14	1	Cardiologie	20	1	Neurologie	20
2	Med. School	16	1	Longziekten	14	2	Longziekten	17	2	Reumatologie	14
3	Neurologie	14	3	Heelkunde	11	3	Neurologie	13	3	Heelkunde	13
						3	Med. School	13			
Top 3: Totale impact factor score als 1e, 2e of laatste auteur:											
1	Cardiologie	110	1	Cardiologie	63	1	Cardiologie	178	1	Cardiologie	90
2	Longziekten	57	2	Neurologie	39	2	Longziekten	99	2	Neurologie	74
3	Neurologie	47	3	Longziekten	37	3	Med. School	44	3	Longziekten	47
Top 3: Gemiddelde impact factor score als 1e, 2e of laatste auteur:											
1	Cardiologie	6.1	1	Gynaecologie	4.6	1	Cardiologie	8.9	1	Cardiologie	12.8
2	Longziekten	5.1	2	Cardiologie	4.6	2	Longziekten	5.8	2	MDL	9.9
3	Microbiologie	4.4	3	Neurologie	3.9	3	Microbiologie	5.2	3	Med. School	6.0

Overzicht aantal publicaties per vakgroep:

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Anesthesiologie	2	1	1	0	0	2	0	1	0	1
Cardiologie	14	23	33	21	25	28	39	31	40	27
Dermatologie	0	0	0	0	0	0	0	0	0	1
Gynaecologie	15	7	5	5	7	6	4	13	7	6
Heelkunde	38	26	24	13	21	31	26	30	20	39
Intensive Care	2	12	16	11	13	14	13	20	15	12
Interne Geneeskunde	13	17	15	16	20	17	8	11	24	14
Kindergeneeskunde	4	7	6	5	3	11	6	6	8	3
Klinische Chemie	14	10	6	2	6	7	5	5	7	4
Klinische Farmacie	3	4	4	4	6	8	10	3	8	13
Klinische Fysica	1	0	0	0	0	2	0	2	1	0
Klinische Psychologie	0	1	4	3	4	1	0	1	2	1
KNO	1	1	0	0	1	1	1	0	0	0
Longziekten	5	17	10	11	12	16	19	24	28	14
MDL	5	4	13	6	11	5	9	10	5	14
Medical School Twente	13	13	27	24	33	35	33	26	24	24
Medische Microbiologie	6	8	5	7	2	2	4	3	1	2
Mond- kaak-, aangez.chirurgie	1	0	1	3	0	0	1	0	1	0
Neurochirurgie	0	0	2	1	5	9	5	5	4	3
Neurologie	23	21	19	34	39	33	41	28	30	33
Nucleaire Geneeskunde	1	0	1	0	0	2	0	0	0	0
Oogheelkunde	0	0	0	0	0	0	0	0	1	0
Orthopedie	2	3	3	0	4	7	5	4	2	5
Pathologie	6	9	12	1	5	8	4	9	3	4
Plastische Chirurgie	1	1	0	2	0	2	4	4	13	12
Psychiatrie	0	0	0	0	0	1	0	4	0	0
Raad van Bestuur	0	0	0	0	0	0	0	0	0	9
Radiologie	11	6	7	6	11	14	10	4	11	2
Radiotherapie	4	5	10	3	5	12	10	4	5	4
Reumatologie	17	25	21	32	20	23	15	7	15	17
Revalidatiegeneeskunde	5	4	11	7	8	6	0	0	1	0
Thoraxchirurgie	2	5	3	4	3	2	4	5	4	3
Urologie	0	0	0	0	0	0	0	0	1	0

Promoties in MST in 2019

Cardiologie

Dual Antiplatelet Therapy After Stenting In All-Comers, ACS Patients And In High Bleeding Risk

Dissertation

to obtain the degree of doctor at the University of Twente,
on the authority of the rector magnificus, prof. dr. T.T.M. Palstra,
on account of the decision of the Doctorate Board,
to be publicly defended
on Friday the 13th of December 2019 at 16.45 hours

by

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Promotor: Prof. dr. C. von Birgelen
Copromotor: Dr. C.J.M. Doggen

Samenvatting
Er is voortdurend onderzoek gaande naar de optimale medische behandeling van patiënten met symptomatisch coronairlijden. In de afgelopen decennia is gebleken dat duale antiplaatjes therapie (d.w.z. een combinatie van aspirine en een andere plaatjesremmer) effectief is bij de behandeling van patiënten die een percutane coronaire interventie met stent implantatie ondergaan. Deze therapie heeft geleid tot een vermindering van nadelige uitkomsten zoals een stent trombose of myocardinfarct. De introductie van nieuwe medicijnen met krachtigere plaatjesremming ten opzichte van het lang gebruikte middel clopidogrel heeft geleid tot veelbelovende resultaten in gerandomiseerde klinische trials. In deze studies, uitgevoerd bij patiënten die behandeld werden voor een acuut coronair syndroom, werd met de krachtigere antiplaatjes therapie een reductie gezien in ischemische eindpunten. Deze gunstige studieresultaten moeten echter in perspectief worden geplaatst. Enerzijds werden de positieve effecten deels tenietgedaan door ongewenste bijwerkingen; zo bleken patiënten die behandeld werden met de nieuwe medicijnen een verhoogd risico te hebben op het optreden van ernstige bloedingen. Daarnaast valt op te merken dat patiënten in klinische trials een geselecteerde groep betreft welke niet altijd representatief hoeft te zijn voor de patiënt uit de dagelijkse praktijk. Om deze redenen is het noodzakelijk de effecten van nieuwe medicijnen separaat te onderzoeken in patiënten die behandeld worden in de dagelijkse praktijk. Dit wordt gedaan in zogenoemde *real world* studies.

Naast de introductie van nieuwe medicijnen kan parallelle ontwikkeling op het gebied van medische hulpmiddelen ervoor zorgen dat eerdere studieresultaten al snel verouderd raken en daarmee niet meer bruikbaar zijn voor in de kliniek. In de afgelopen jaren is er een belangrijke ontwikkeling geweest in de verbetering van medicijn-afgevende coronaire stents waardoor de effectiviteit en veiligheid van een percutane coronaire interventie zijn toegenomen. Het resultaat van deze progressie in stent technologie zou ertoe kunnen leiden dat de eerder gevonden voordelen van de nieuwere plaatjesremmers niet of nauwelijks aanwezig zijn in patiënten die behandeld worden met nieuwe generatie medicijn-afgevende stents. De nadelige effecten van de nieuwe krachtige plaatjesremmers blijven echter wel bestaan.

Artsen zullen patiënten zoveel mogelijk behandelen op basis van beschikbare data uit wetenschappelijke klinische studies. Bepaalde subgroepen van patiënten zouden baat kunnen hebben bij een meer op maat gesneden behandeling, rekening houdend met het individuele risicoprofiel en de behoeften van een specifieke patiënt. Eén van deze subgroepen betreft patiënten met coronairlijden en een hoog bloedingsrisico. Deze groep bevat patiënten met een bijzonder hoog risico op ernstige bloedingen maar ook op recidiverende ischemische complicaties.

In dit proefschrift worden patiënten met een acuut coronair syndroom onderzocht die een percutane coronaire interventie ondergaan met implantatie van huidige generatie medicijn-afgevende stents. Op deze manier wordt de impact van de aanbevelingen uit internationale richtlijnen onderzocht die de afgelopen jaren gewijzigd zijn en tegenwoordig duale antiplaatjes therapie met ticagrelor aanraden in plaats van met clopidogrel (naast aspirine). Speciale aandacht wordt besteed aan de klinische uitkomsten van patiënten met een hoog bloedingsrisico, aangezien deze belangrijke subgroep onderbelicht is in veel klinische studies. Daarnaast worden de effectiviteit en veiligheid van huidige medicijn-afgevende stents onderzocht in gerandomiseerde

klinische studies met zeer beperkte exclusiecriteria, zogenoemde *all-comers* studies. Hierbij ligt de nadruk op de klinische uitkomsten na het eerste jaar na stent implantatie aangezien Nederlandse cardiologen in het algemeen de duale antiplaatjes therapie stoppen na één jaar en vervolgens alleen de aspirine continueren.

Hoofdstuk 1 geeft achtergrondinformatie over coronaire hartziekten en het acuut coronair syndroom. Daarnaast wordt een korte uiteenzetting gegeven over de ontwikkeling van coronaire stents en de ontwikkeling van antiplaatjes therapie met het daarbij samengaande risico op bloedingscomplicaties.

Hoofdstuk 2 presenteert de primaire uitkomsten van de *real world* CHANGE DAPT studie. Er werden 2.062 patiënten geïncludeerd die behandeld werden voor een acuut coronair syndroom met de huidige generatie medicijn-afgevende stents. Inclusie vond plaats gedurende twee opeenvolgende studieperiodes. Patiënten werden tijdens de eerste periode primair behandeld met duale antiplaatjes therapie bestaande uit aspirine en clopidogrel en in de tweede periode met duale antiplaatjes therapie bestaande uit aspirine en ticagrelor. Het door de nieuwe richtlijnen aanbevolen ticagrelor bleek geassocieerd met hogere risico's, wat werd teruggezien in het primaire eindpunt *net adverse clinical and cerebral events* (5.1% vs. 7.8%). Het verschil in dit gecombineerde eindpunt werd voornamelijk gedreven door het aantal ernstige bloedingen (1.2% vs. 2.7%), terwijl er geen significant verschil werd gevonden in ischemische eindpunten.

Hoofdstuk 3 beschrijft de mortaliteit van de CHANGE DAPT deelnemers twee jaar na stent implantatie. De resultaten tonen lage sterftecijfers in de clopidogrel groep (4.7%) en in de ticagrelor groep (4.3%) zonder significante verschillen tussen beide groepen. De bevindingen bleken consistent in zowel patiënten met een hoog bloedingsrisico (13.6% vs. 10.6%) als in patiënten zonder hoog bloedingsrisico (1.8% vs. 1.7%).

Hoofdstuk 4 richt zich op de patiënten met een hoog bloedingsrisico in de CHANGE DAPT studie. Van alle deelnemers had 26.5% een hoog bloedingsrisico. In deze populatie bleek dat, ten opzichte van patiënten in de clopidogrel groep, patiënten in de ticagrelor groep een significant hoger risico hebben op het krijgen van een ernstige bloeding (1.7% vs. 5.0%). Het risico op een ernstige bloeding in patiënten zonder hoog bloedingsrisico bleek na één jaar gelijk te zijn voor patiënten behandeld in de clopidogrel groep en in de ticagrelor groep (1.1% vs. 1.7%). Er werd geen verschil gevonden in ischemische eindpunten tussen de clopidogrel groep en de ticagrelor groep voor zowel patiënten met een hoog als een niet-hoog bloedingsrisico.

In **hoofdstuk 5** onderzoeken we de effectiviteit en veiligheid van medicijn-afgevende stents met verschillende soorten polymeren in de behandeling van patiënten met een hoog bloedingsrisico die deelnamen aan de BIO-RESORT trial. Patiënten ondergingen een percutane coronaire interventie met implantatie van stents met een biologisch afbreekbare polymeer of stents met een permanente polymeer. Bij ongeveer 30% van de 3.514 *all-comers* in BIO-RESORT bleek er sprake van een hoog bloedingsrisico. Beide stentgroepen bleken vergelijkbaar te presteren op het gebied van effectiviteit en veiligheid één jaar na stent implantatie. Er werd geen significant verschil gevonden tussen de stentgroepen met betrekking tot het primaire

samengestelde eindpunt *target vessel failure* (6.5% vs. 7.3%) en alle vooraf gespecificeerde secundaire klinische eindpunten.

Hoofdstuk 6 beschrijft de klinische uitkomsten van alle 3.514 patiënten die deelnamen aan de BIO-RESORT trial twee jaar na stent implantatie. In deze studie werden *all-comers* gerandomiseerd naar behandeling met één van twee soorten medicijn-afgevende stents met een biologisch afbreekbare polymeer (de Orsiro stent of de Synergy stent) of een medicijn-afgevende stent met een permanente polymeer (de Resolute Integrity stent). Deelnemende patiënten volgden een strikt beleid omtrent het stoppen met duale antiplaatjes therapie één jaar na de percutane interventie. De effectiviteit en veiligheid van beide stents met een biologisch afbreekbare polymeer was twee jaar na interventie vergelijkbaar met de stent met een permanente polymeer. Een landmark analyse suggereerde dat de Orsiro stent het risico op een herhaalde revascularisatie gedurende het tweede jaar reduceert ten opzichte van de Resolute Integrity stent.

Hoofdstuk 7 rapporteert het primaire eindpunt van de internationale, gerandomiseerde BIONYX trial. In BIONYX werden 2.488 *all-comer* patiënten gerandomiseerd naar behandeling met medicijn-afgevende stents bestaande uit samengesteld metaal met een permanente polymeer (de Resolute Onyx stent) of met medicijn-afgevende stents bestaande uit kobalt-chroom met een biologisch afbreekbare polymeer (de Orsiro stent). De nieuwe Resolute Onyx stent werd hiermee voor het eerst in een gerandomiseerde klinische studie vergeleken met een andere stent en bleek niet inferieur ten opzichte van de Orsiro stent ten aanzien van het primaire gecombineerde eindpunt *target vessel failure* (4.5% vs. 4.7%). Een opvallende bevinding was het erg lage aantal gevallen van stent trombose in patiënten die behandeld werden met de Resolute Onyx stent (0.1% vs. 0.7%).

Hoofdstuk 8 presenteert de lange termijn uitkomsten van de 1.811 *all-comer* patiënten die deelnamen aan de DUTCH-PEERS studie. Deelnemers aan deze studie werden gerandomiseerd naar behandeling met medicijn-afgevende stents bestaande uit kobalt-chroom met een permanente polymeer (de Resolute Integrity stent) of medicijnafgevende stents bestaande uit platina-chroom met een permanente polymeer (de Promus Element stent). Vijf jaar na implantatie lieten beide stents vergelijkbare resultaten zien met betrekking tot effectiviteit en veiligheid. Het aantal gevallen van *target vessel failure* (13.2% vs. 14.2%) en stent trombose (1.5% vs. 1.3%) bleek vergelijkbaar.

In **hoofdstuk 9** illustreren we het belang van lange termijn follow-up van patiënten die zijn geïncludeerd in coronaire stent studies in een commentaar op de vijf jaar uitkomsten van de gerandomiseerde BIOSCIENCE trial.

Hoofdstuk 10 presenteert de algemene discussie van de bevindingen van dit proefschrift. Daarnaast wordt een visie gegeven op te verrichten onderzoeken in de toekomst.

Conclusies
Er heeft een indrukwekkende ontwikkeling plaats gevonden in de behandeling van patiënten met coronaire hartziekten. Tegenwoordig worden vrijwel alle percutane coronaire interventies uitgevoerd met het plaatsen van medicijn-afgevende stents.

Deze stents zijn bewezen effectief gebleken in het reduceren van de incidentie van nieuwe vernauwingen ter plaatse van de initiële laesie. Daarnaast is aangetoond dat de huidige generatie medicijn-afgevende stents veilig zijn met een laag risico op cardiale dood en een zeer laag risico op stent trombose na één jaar. Tevens blijkt uit onze resultaten dat de effectiviteit en veiligheid van deze stents ook op lange termijn behouden blijft.

Simultaan aan de innovatie in medicijn-afgevende stents heeft er een ontwikkeling plaats gevonden in de antitrombotische behandeling van patiënten met een acuut coronair syndroom en na coronaire stent implantatie. Duale antiplaatjes strategieën met verschillende medicijnen (naast aspirine) werden onderzocht.
Uit gerandomiseerde klinische studies is gebleken dat krachtige antiplaatjes medicijnen zoals ticagrelor het risico op ischemische uitkomsten verlagen ten opzichte van behandeling met clopidogrel. Deze studies werden echter uitgevoerd in patiënten die niet altijd behandeld werden met een percutane interventie en bij de patiënten die wel een percutane interventie ondergingen werden voornamelijk oudere generatie stents gebruikt. Ons eigen onderzoek suggereert dat de noodzaak tot krachtige antiplaatjes therapie minder noodzakelijk is in patiënten die behandeld worden met de huidige generatie medicijn-afgevende stents.

Deze resultaten kunnen van groot belang zijn voor patiënten met een acuut coronair syndroom die een verhoogd bloedingsrisico hebben. Ondanks dat deze patiënten ook een verhoogd risico lopen op recidiverende ischemische complicaties laat ons onderzoek zien dat deze hoog risico subgroep voornamelijk te lijden heeft van ernstige bloedingen welke geassocieerd zijn met de krachtige antiplaatjes therapie. De huidige observaties van onze studies, in combinatie met de bevindingen van anderen, zal artsen motiveren om patiënten met een verhoogd risico te identificeren. Op deze manier kan iedere individuele patiënt de optimale behandelingsstrategie krijgen waarbij een balans wordt gezocht tussen enerzijds het risico op ischemische complicaties en anderzijds het risico op bloedingen. Resultaten van voortschrijdend onderzoek naar nieuwe antitrombotische strategieën zoals de-escalatie van krachtige naar minder krachtige plaatjesremmers of een farmaco-genetische benadering zouden in de toekomst gebruikt kunnen worden bij de besluitvorming ten aanzien van de optimale medicamenteuze behandeling van iedere individuele patiënt.

Heelkunde

On evaluating stent-artery interaction in abdominal aortic stent grafting
An in-depth analysis of longitudinal and pulsatility related behavior

Dissertation

to obtain the degree of doctor at the University of Twente,
on the authority of the rector magnificus,
Prof.dr. T.T.M. Palstra,
on the account of decision of the graduation committee,
to be publicly defended on
Friday, November 1st 2019 at 14.45 hours

by

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Supervisor: Prof.dr. R.H. Geelkerken
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Samenvatting
Een aneurysma is een uitpuiling of opzwelling in de wand van een bloedvat. Meestal ontstaat een aneurysma als gevolg van slagaderverkalking die de wand van het bloedvat verzwakt. Als de verwijding zich bevindt in het in de buik gelegen gedeelte van de aorta, wordt dit een aneurysma aorta abdominalis (AAA) genoemd. In de loop der tijd verliest de vaatwand zijn elasticiteit waardoor de vaatwand kan scheuren door de kracht van een normale bloeddruk in het aneurysma.
In verschillende onderzoeken is aangetoond dat het uitschakelen van het aneurysma door het plaatsen van een endoprothese (een kunststof vaatprothese met metalen stents) via de lies (endovasculair aorta reparatie) op korte termijn betere resultaten geeft dan de conventionele en belastende open chirurgische methode. Echter, op lange termijn hebben 10-20% van de patiënten een reinterventie nodig door falen van de endoprothese (scheuren van de vaatwand, lekkage van bloed langs de endoprothese in het aneurysma, of het afsluiten van bloedstroom door de endoprothese). Falen kan onder andere gerelateerd zijn aan structurele schade aan de endoprothese, verwijding van de aorta door progressie van de ziekte, en het losraken van de endoprothese van de vaatwand onder invloed van het pulserende bloedvat.
Om de lange termijn uitkomsten te verbeteren is meer inzicht nodig in het gedrag van geïmplanteerde endoprothesen, om de best passende endoprothese te kunnen kiezen voor een patiënt en om het ontwerp van endoprothesen te verbeteren. In dit proefschrift zijn onderzoeksmethoden ontwikkeld, gevalideerd en toegepast om de voortgaande interactie tussen endoprothese en bloedvat te onderzoeken op basis van hartslag gekoppelde computer tomografie (CT) scans.
In dit proefschrift is hoofdzakelijk onderzoek gedaan naar een patiënt cohort dat behandeld is met een Anaconda AAA endoprothese en tot 2 jaar na interventie is gevolgd met hartslag gekoppelde CT-scans. In het eerste deel van het proefschrift zijn veranderingen in geometrie van de endoprothese en de aorta onderzocht gedurende follow-up. Het tweede deel richt zich op bewegingen van de endoprothese die ontstaan tijdens de hartslag. Hierin is ook onderzoek gedaan naar bewegingen van een ander type endoprothese (Nellix endoprothese) die gebruik maakt van een polymeer zak om het aneurysma in zijn geheel af te sluiten van de bloedstroom (endovasculair aneurysma sealing).

Deel 1: Veranderingen in geometrie na verloop van tijd
De Anaconda endoprothese heeft 2 Nitinol stent ringen bovenin de endoprothese die zich ontvouwen als een zadelvorm na ontplooiing van de endoprothese via de lies. Doordat de diameter van de ringen groter gekozen wordt dan de diameter van de aorta (‘oversizing’), drukken de ringen tegen de vaatwand waarmee het aneurysma uitgeschakeld wordt van de bloedstroom (‘sealing’).

In **hoofdstuk 2** is onderzocht in hoeverre de diameter van de ringen uitzet gedurende de periode na implantatie van de endoprothese. Gedurende de 1^{e} maand vonden reeds grote veranderingen plaats waarna binnen 6 maanden de ringen waren uitgezet tot nabij de nominale ring diameter (1^{e} ring 97%, 2^{e} ring 95%). Dit betekent dat de mate van oversizing gevolgen heeft voor de verwijding van de aorta ter hoogte van de ringen. Verder is geobserveerd dat de ringen zich asymmetrisch kunnen vormen naar de vorm van de aorta maar dat uiteindelijk de ringen weer een ronde vorm aannemen.

In **hoofdstuk 3** is onderzocht of het uitzetten van de ringen ook leidt tot het verwijden van de aorta aangrenzend aan de ringen. Uit deze studie is gebleken dat onder de stent ringen de aorta diameter stabiel bleef of af nam in de meeste patiënten waar een toename in diameter werd gezien in gevallen waar de endoprothese zich naar beneden verplaatste. Boven de stent ringen bleef de aorta diameter onveranderd. Deze bevindingen impliceren dat bepaalde pati¨enten mogelijk minder follow-up nodig hebben waar anderen een groter risico lopen op falen en dus nauwlettender gevolgd zouden moeten worden.
De verandering van de zadelvorm door het uitzetten van de ringen heeft mogelijk ook gevolgen voor de positie van de ringen in de aorta ten opzichte van de nierslagaders. Bij implantatie worden de ringen ontplooid net onder de aftakking van de nierslagaders. Door de zadelvorm is het echter mogelijk om de ringen met de pieken van de zadelvorm ter hoogte van de nierslagaders te plaatsen terwijl de dalen van de zadelvorm zich onder de nierslagaders bevinden en de nierslagaders daarmee niet worden afgesloten van bloedstroom.

In **hoofdstuk 4** is de verplaatsing van de pieken en dalen van de zadelvorm onderzocht. Voornamelijk de pieken bleken omlaag te verplaatsen bij het afvlakken van de zadelvorm. Ook kwamen schuin geplaatste ringen (onder een hoek ten opzichte van de as van de aorta) meer recht te liggen. De dalen kwamen met maximaal 3 mm omhoog alleen in gevallen waar veel oversizing was toegepast (>30% t.o.v. de aorta diameter). Deze bevindingen suggereren dat het afvlakken van de zadelvorm geen risico vormt voor het afsluiten van de nierslagaders, waarbij een plaatsing van de dalen aanliggend aan de nierslagaders een veilige techniek is indien gematigde oversizing wordt toegepast (10-20%).

Hoofdstuk 5 richt zich op de 2 pootjes van de Anaconda endoprothese, welke voorbij het aneurysma een stukje doorlopen in de arteria iliaca communis (gemeenschappelijke heupslagader). Thrombus (bloedstolsel) vorming in de pootjes kan leiden tot het afsluiten van de bloedstroom naar de bil en benen waardoor reinterventie nodig is. De pootjes bestaan uit kunststof met ongeveer elke 5 mm een stent ring. Veranderingen in de configuratie van de pootjes kunnen leiden tot het naar binnen vouwen van de kunststof en daarmee mogelijk bijdragen aan thrombus vorming. Gedurende follow-up zijn een toename in curvatuur, een afname in poot lengte en een afname in afstand tussen de ringen in de pootjes geobserveerd. Deze inzichten kunnen bijdragen aan het voorspellen van poot afsluiting en het verbeteren van het ontwerp van de endoprothese.

Deel 2: Hartcyclus gerelateerd gedrag
Er is weinig bekend over het dynamische gedrag van geïmplanteerde endoprothesen, hoewel dit van groot belang is voor het ontwikkelen van duurzame endoprothesen. De bloedstroom induceert zo'n 40 miljoen cycli per jaar waaraan de endoprothese–aorta combinatie wordt blootgesteld. Hiermee wordt de positiestabiliteit van de endoprothese en de sealing op de proef gesteld maar ook de mechanische stabiliteit van de endoprothese.

In **hoofdstuk 6** hebben we een eerder ontwikkeld algoritme geïmplementeerd om de nauwkeurigheid van geanalyseerde endoprothese bewegingen in hartslag gekoppelde CT-scans te evalueren. Deze methode combineert beeldregistratie en segmentatie technieken. Een fantoom opstelling met een gecontroleerd bewegende

endoprothese werd gebruikt. De grootst bepaalde fout op de verplaatsing was 0.3 mm. De analyse methode werd verder succesvol toegepast op 4 klinische casussen met elk een ander type endoprothese.

In **hoofdstuk 7** is deze methode toegepast om de beweging en vervorming van de 2 Anaconda sealing ringen te onderzoeken tijdens de hartslag. Een radiale expansie en contractie van de ringen van <3.5% diameter verandering werd vastgesteld, wat gunstig is voor de positiestabiliteit en het risico op metaalmoeheid reduceert. De mogelijke gevolgen van het dempen van het natuurlijk pulseren van de aorta zijn echter onduidelijk. De methode zoals beschreven in deze studie maakt het mogelijk om locaties op de stents te identificeren die het meest vatbaar zijn voor dynamische spanning door het cyclisch buigen. Dit werk biedt een basis voor verbeterde spanningsrek analyses, duurzaamheidstests en ontwerp verificatie.

In **hoofdstuk 8** zijn hartslag gerelateerde bewegingen van de Nellix endoprothese onderzocht om inzicht te krijgen in de stabiliteit van de configuratie waarin naast de 2 standaard parallelle stents ook stents werden geplaatst in de nier- en/of darmslagaders. Bewegingen tijdens de hartslag waren minimaal. De afstand tussen endoprothese onderdelen veranderde ten hoogste 0.4 mm, de buiging van de stents in de nier/darmslagaders was ten hoogste 2.6° en de hoek tussen de endoprothese onderdelen veranderde ten hoogste 1.7°. Deze observaties demonstreren een stabiele situatie tijdens de hartslag. Desalniettemin zijn de parameters zoals gemeten in deze studie relevant voor follow-up. Na verloop van tijd kunnen bewegingen van endoprothese onderdelen veranderen onder invloed van trekkrachten door de bloedstroom, wat kan leiden tot neerwaartse verschuiving en lekkage van bloed langs de polymeer zak, de meest voorkomende complicatie bij endovasculair aneurysma sealing.
Het ontwikkelen van kwantitatieve methoden vraagt ook om evaluatie en validatie van de methode voor de beoogde toepassing. Het valideren van een registratie algoritme is ingewikkeld doordat in de beelddata de daadwerkelijke bewegingen niet bekend zijn. De fantoom experimenten zoals toegepast in hoofdstuk 6 zijn erg waardevol voor het bepalen van de nauwkeurigheid en gevoeligheid van de meetmethode maar zijn tegelijk ook een vereenvoudiging van de werkelijke complexe bewegingen die in het lichaam plaatsvinden.

In **hoofdstuk 9** wordt een wiskundige aanpak beschreven om de nauwkeurigheid van beeldregistratie te evalueren door klinische beelddata kunstmatig te vervormen.

Slotopmerkingen
De methoden zoals beschreven in dit proefschrift maken het mogelijk om endoprothese–aorta interactie te volgen gedurende follow-up op basis van hartslag gekoppelde CT-scans. De inzichten verkregen in dit proefschrift dragen bij aan beter geïnformeerde klinische besluitvorming omtrent endoprothese selectie, positionering en controles. Daarnaast kunnen de verkregen inzichten leiden tot aanpassingen aan het ontwerp van endoprothesen waardoor in de toekomst de kans op complicaties zou kunnen verminderen. Dit werk ondersteunt het ontwikkelen van realistischere preklinische tests en het ontwikkelen van duurzame endoprothesen.

Heelkunde

Traditional And Novel Diagnostic Techniques To Assess Wound Infection

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Twente,
op gezag van de rector magnificus,
prof. dr. T.T.M. Palstra,
volgens besluit van het College voor Promoties
in het openbaar te verdedigen
op vrijdag 22 maart 2019 om 12:45 uur

door

Maartje Theodora Haalboom
geboren op 25 augustus 1990
te Veenendaal, Nederland

Promotor: Prof. dr. J. van der Palen
Copromotor: Dr. R.J. Beuk

Samenvatting
Een groot deel van de patiënten in de gezondheidszorg heeft één of meerdere slecht genezende wonden. Een grote complicatie voor patiënten met slecht genezende wonden is het ontwikkelen van een wondinfectie. Een wondinfectie ontstaat wanneer pathogenen in de wond krachtiger zijn dan het immuunsysteem. Zowel de activiteit van de pathogenen zelf als de interactie tussen de pathogenen en het immuunsysteem zorgen ervoor dat de weefsels in en rondom de wond verder worden aangetast. Dit resulteert in een verdere vertraging van het genezingsproces, maar kan ook leiden tot ernstigere complicaties zoals verspreiding van de infectie naar de bloedsomloop of de noodzaak tot amputatie. Daarom is het essentieel om wondinfectie nauwkeurig en op tijd op te kunnen sporen. Anderzijds kan het nauwkeurig uitsluiten van wondinfectie het onnodig gebruik van antibiotica voorkomen. Het doel van dit proefschrift was om traditionele en nieuwe diagnostische methoden voor het nauwkeurig en tijdig opsporen van wondinfectie te evalueren.

De traditionele diagnostische methoden zijn voornamelijk gebaseerd op het (subjectief) interpreteren van klinische informatie en microbiologische kweekresultaten.

In **hoofdstuk 3** beschrijven we een onderzoek waarin we bepalen of er verschil is in de microbiologische kweekresultaten van twee bekende technieken om wondmateriaal te verzamelen: de wonduitstrijk en het wondbiopt. Bij 180 patiënten hebben we met beide technieken wondmateriaal afgenomen en volgens standaardprocedures laten kweken in het microbiologisch laboratorium. We vonden geen betekenisvolle verschillen tussen kweekresultaten van de wonduitstrijk en het wondbiopt. In 73% van alle wonden konden we vanuit een wonduitstrijk dezelfde (mogelijk) pathogene micro-organismen kweken als vanuit het biopt. Voor specifieke micro-organismen waren de kweekresultaten tussen de wonduitstrijk en het biopt gelijk in 87-98% van alle wonden. Het lijkt daarom in de klinische praktijk niet noodzakelijk om een invasief biopt af te nemen voor een microbiologische kweek. Voor het beoordelen van wondinfectie is het echter noodzakelijk om (klinische informatie en) microbiologische kweekresultaten te interpreteren.

Daarom hebben we in **hoofdstuk 4** onderzocht of de beoordeling van wondinfectie verschilt tussen de situatie waarin, naast klinische informatie over de wond, kweekresultaten van een wonduitstrijk of van een biopt beschikbaar zijn. Daarvoor hebben we de kweekresultaten van de 180 patiënten uit het onderzoek in hoofdstuk 3 aangevuld met klinische informatie. Een panel van 6 experts heeft vervolgens, onafhankelijk van elkaar, iedere wond beoordeeld als geïnfecteerd of niet, apart voor de situatie waarin kweekresultaten van de wonduitstrijk of het biopt beschikbaar waren. We vonden geen significante verschillen in de beoordelingen tussen de wonduitstrijk en het biopt. Er waren echter wel substantiële verschillen tussen de beoordelingen van de verschillende experts; in 34% (wonduitstrijk) en 42% (biopt) van de wonden gaven de experts dezelfde beoordeling. Deze variabiliteit tussen de verschillende experts kan het nauwkeurig opsporen van wondinfectie bemoeilijken.

Om een oplossing te bieden voor de nadelen van de traditionele methoden zijn verschillende nieuwe diagnostische methoden voor het opsporen van wondinfectie ontwikkeld. In dit proefschrift worden drie veelbelovende technieken geëvalueerd.

In **hoofdstukken 5 en 6** evalueren we een nieuwe diagnostische techniek gebaseerd op het meten van de activiteit van bepaalde enzymen die door het immuunsysteem worden uitgescheiden om te helpen bij de afweer tegen pathogenen. In hoofdstuk 5 laten we in een onderzoek met 81 patiënten met verschillende wonden zien dat een verhoogde activiteit van myeloperoxidase (MPO), lysozyme en humaan neutrofiel elastase (HNE) een veelbelovende marker voor wondinfectie is. Bovendien kan de testmethode binnen 30 minuten resultaat geven. De studie laat verder zien dat de diagnostische nauwkeurigheid van de test wordt vergroot wanneer de metingen van de verschillende enzymen worden gecombineerd tot 1 resultaat. Daarom hebben we in hoofdstuk 6 een diagnostische test onderzocht waarin we de metingen van de drie enzymen hebben gecombineerd. De diagnostische test gaf sneller resultaat (<20 min.), maar bleek een lagere diagnostische nauwkeurigheid te hebben dan verwacht op basis van de resultaten in hoofdstuk 5. Dit verschil kan mogelijkerwijs verklaard worden door (chemische) veranderingen in de manier waarop enzymactiviteit wordt gemeten, of door het gebruik van verschillende referentiestandaarden voor het bepalen van de infectie status van de wond. De referentiestandaard in deze studie was gebaseerd op de (subjectieve) interpretatie van klinische en microbiologische informatie, terwijl de referentiestandaard in hoofdstuk 5 alleen gebaseerd was op microbiologische kweekresultaten. Doordat er geen perfecte referentiestandaard beschikbaar is zou het ook kunnen dat het hoge aantal fout positieve resultaten van de diagnostische test in werkelijkheid een indicatie geeft dat de test wondinfectie in een vroeg stadium op kan sporen, voordat klinische symptomen geobserveerd kunnen worden.

In **hoofdstuk 7** onderzoeken we of het meten van de pH van een wond als makkelijke, goedkope en snelle manier kan dienen om wondinfectie op te sporen. In een studie met 120 patiënten laten we zien dat bij een toenemende wond pH, het aantal wonden dat als geïnfecteerd wordt beoordeeld door ervaren artsen ook toeneemt. De pH van geïnfecteerde wonden was gemiddeld 7.2 tegenover een gemiddelde pH van 6.5 voor niet-geïnfecteerde wonden. Een toenemende enzymactiviteit van MPO, lysozyme en HNE was ook geassocieerd met een toenemende wond pH. Echter is vervolgonderzoek nodig om de relatie tussen wond pH en wondinfectie beter te kunnen onderbouwen, en om alternatieve verklaringen uit te kunnen sluiten.

In **hoofdstuk 8** beschrijven we een verkennend onderzoek naar de mogelijkheid om een elektronische neus, het Aetholab, te gebruiken voor het opsporen van wondinfectie. Het Aetholab meet vluchtige organische stoffen (volatile organic compounds, VOC's) van patiëntmaterialen, terwijl het bijbehorende geavanceerde softwarepakket gebruikt kan worden om onderscheid te kunnen maken tussen metingen die wel of niet bij een specifieke ziekte passen. Wij hebben Aetholab gebruikt om wonduitstrijken van 77 patiënten te analyseren en vonden een redelijk goede diagnostische nauwkeurigheid bij het gebruik van verschillende referentiestandaarden voor wondinfectie, die gebaseerd waren op klinische

informatie en microbiologische kweekuitslagen. In 71-87% van de wonden gaf het Aetholab dezelfde beoordeling van wondinfectie als de referentiestandaarden. Deze veelbelovende eerste resultaten zijn bemoedigend voor het opstarten van een grotere studie waarin we de algoritmes van de elektronische neus willen verbeteren en valideren. Verder is het doel om te onderzoeken of het mogelijk is alternatieve uitkomsten te koppelen aan de Aetholab metingen, zoals het detecteren van micro-organismen.

De nieuwe diagnostische methoden die in dit proefschrift zijn geëvalueerd hebben de potentie om wondinfectie op een snelle en makkelijke manier op te sporen. De technieken geven binnen 20 minuten resultaat en maken bij het analyseren gebruik van een wonduitstrijk, dat een makkelijke, goedkope en niet-invasieve methode is om wondmateriaal af te nemen. Bovendien zouden de testen de variabiliteit in de traditionele beoordeling van wondinfectie kunnen verminderen. Het is echter lastig om de nauwkeurigheid van een nieuwe techniek te bepalen wanneer er geen methode is om de werkelijke infectie status van de wond te bepalen. Om toch een beeld te kunnen geven van de diagnostische nauwkeurigheid van de nieuwe technieken hebben we in dit proefschrift gebruik gemaakt van de beste referentiestandaarden die beschikbaar waren. Het doel is om de resultaten uit dit proefschrift in grotere studies te verifiëren en om mogelijk ook alternatieve methoden te gebruiken om de diagnostische nauwkeurigheid te bepalen. We hopen echter dat de resultaten uit dit proefschrift er voor zorgen dat professionals in de wondzorg zich meer bewust zijn over de imperfecties die bestaan in de diagnostische methoden die momenteel gebruikt worden om wondinfectie vast te stellen. Ondanks de onzekerheid over de exacte diagnostische nauwkeurigheid kan het waardevol zijn om veelbelovende nieuwe technieken te gebruiken als ondersteuning bij het beoordelen van wondinfectie.

Klinische Farmacie

Descriptive Pharmacokinetics and Physiologically Based Predictions of Paracetamol and Its Metabolites in Special Populations

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof. Dr. R.C.M.E. Engels
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
dinsdag 22 oktober 2019 om 15:30 uur

door

Paola Mian
geboren te Gouda in 1990

Promotoren**:** Prof. dr. D. Tibboel
Prof. dr. K.M. Allegaert

Samenvatting

De studies in deze thesis richten zich op het beschrijven van de farmacokinetiek (PK) van paracetamol (acetaminophen, APAP) in specifieke patiëntenpopulaties, waaronder foetussen, neonaten, kinderen, zwangere vrouwen en ouderen. Inzicht in PK is de eerste stap die nodig is voordat de relatie tussen PK en farmacodynamiek (PD) kan worden bestudeerd, om uiteindelijk te onderzoeken of doseringsaanpassingen nodig zijn in deze specifieke patiëntenpopulaties.

Sectie I. Algemene introductie en achtergrondinformatie

Hoofdstuk 1 geeft een overzicht van de achtergrondinformatie over paracetamol (bijv. werkingsmechanisme en doseringsvoorschriften volgens de labels) en de fysiologische verschillen die de PK en de variabiliteit van paracetamol kunnen beïnvloeden. Daarnaast worden ook de farmacometrische technieken, die gebruikt worden om de PK van paracetamol te beschrijven, belicht.

Hoofdstuk 2 beschrijft een bepalingsmethode voor paracetamol en zijn metabolieten in plasma met behulp van *ultraperformance liquid chromatography-electrospray ionization-tandem mass spectrometry (UPLC-MS/MS).* Met deze bepalingsmethode kunnen paracetamol en zijn zes metabolieten: paracetamol-glucuronide, -sulfaat, -cysteïne, -glutathion, -mercapturaat, en uit eiwit verkregen paracetamol-cysteïne in menselijk plasma gekwantificeerd worden. De sterkte van de methode is dat er slechts een injectievolume van 10 µL nodig is, de looptijd slechts 4,5 minuten bedraagt en de voorbewerking van het monster eenvoudig is. De bepalingsmethode kon succesvol gevalideerd worden op o.a. patiëntenmonsters en kan in de kliniek worden toegepast voor het meten van concentratietijd data van zowel paracetamol en zijn metabolieten in specifieke patiëntenpopulaties.

Hoofdstuk 3 rapporteert over intermitterende versus continue toediening van paracetamol. Eén onderzoek vergeleek de PK en PD van continue versus intermitterend toegediende paracetamol in gezonde vrijwilligers. Dit onderzoek rapporteerde dat de mediaan plasma concentraties niet verschilden tussen de twee toedieningen, maar pijnstilling alleen bereikt werd met de intermitterende toediening. Daarom is een herbeoordeling van de PK/PD van paracetamol in gestandaardiseerde en gevalideerde experimentele pijnmodellen in gezonde vrijwilligers vereist, voordat continue toediening van paracetamol kan worden overwogen. Totdat deze kennishiaten zijn opgelost, zouden clinici paracetamol intermitterend volgens label moeten toedienen, vooral in de heterogene specifieke patiëntenpopulaties.

Sectie II. Neonaten en kinderen

Hoofdstuk 4 geeft een overzicht van gerapporteerde onderzoeken met een PK-gebaseerd doseringsvoorschrift van paracetamol voor pijnstilling in neonaten, verkregen via een systematische zoekstrategie. Daarnaast is veiligheidsinformatie vermeld in deze onderzoeken verzameld. Met deze PK-gebaseerde doseringsvoorschriften in typische neonaten werden simulaties uitgevoerd waarbij een pijnstillende target concentratie (C_{ssmean}) van 10 mg/L werd gebruikt. Op basis van de uitkomsten werd een doseringsvoorschrift geselecteerd dat voldeed aan de vereisten om de target concentratie te bereiken. Dit resulteerde in een oplaaddosis

van 20 mg/kg, gevolgd door onderhoudsdosering van 10 mg/kg elke 6 uur voor neonaten geboren na een zwangerschapsduur (GA) van 32-44 weken.
Dit doseringsvoorschrift wordt ook ondersteund door korte termijn veiligheidsinformatie. Neonaten geboren na een GA van < 32 weken lijken met een oplaaddosis van 12 mg/kg en een onderhoudsdosis van 6 mg/kg elke 6 uur de target C_{ssmean} te bereiken, hoewel aanvullende klinische onderzoeken moeten aantonen of dit doseringsvoorschrift veilig en werkzaam is.

Hoofdstuk 5 beschrijft de PK van paracetamol en zijn metabolieten bij kinderen na een hartoperatie met gebruik van een cardiopulmonale bypass. In dit onderzoek werden kinderen met en zonder het syndroom van Down onderzocht. De klaring (CL) van paracetamol na een hartoperatie bij een typisch kind van 6,1 kg was 0,96 L/uur en het distributievolume (Vd) bedroeg 7,96 L. De CL van paracetamol en zijn metabolieten nam lineair toe met lichaamsgewicht. Noch het syndroom van Down, noch andere covariaten hadden invloed op de PK parameters van paracetamol en zijn metabolieten. Wanneer we onze bevindingen vergeleken met de resultaten die gerapporteerd werden in de literatuur van leeftijdsgenoten die een andere (niet-hart) operatie hadden ondergaan, bleek dat de CL van paracetamol bij kinderen na een hartoperatie met gebruik van een cardiopulmonale bypass lager en het Vd hoger was. Of deze verschillen in PK ook de noodzaak tot dosisaanpassing rechtvaardigen hangt af van de relatie tussen blootstelling, werkzaamheid en veiligheidsparameters na beide soorten operaties.

Sectie III. Zwangere vrouwen en foetus

Hoofdstuk 6 beschrijft de voorspelling van de PK van paracetamol en zijn metabolieten met behulp van fysiologisch-gebaseerd farmacokinetisch (PBPK) modelleren bij zwangeren. Het doel van dit onderzoek was het vergelijken van paracetamolconcentraties bij steady state (C_{ssmean}), als een marker voor werkzaamheid, en N-acetyl-p-benzoquinone imine (NAPQI) vorming, als een marker voor mogelijke hepatotoxiciteit, met aandacht voor trimester specifieke schattingen tijdens de zwangerschap. De voorspellingen (na toediening van 1000 mg paracetamol) resulteerden in de laagste C_{ssmean} in de derde trimester populaties (4,5 mg/L), terwijl de C_{ssmean} respectievelijk 6,7 mg/L, 5,6 mg/L en 4,9 mg/L waren in de niet-zwangere, eerste en tweede trimester populaties. Uitgaande van een constant verhoogde activiteit van cytochroom-P-450 (CYP)2E1 tijdens de zwangerschap waren de molaire fracties van paracetamol omgezet naar NAPQI het hoogst gedurende het eerste (11%), gevolgd door het tweede (9%) en derde trimester (8,2%), vergeleken met niet-zwangere vrouwen (7,1%). Gezien de hogere productie van NAPQI tijdens de zwangerschap zouden zwangere vrouwen een hoger risico kunnen lopen op paracetamol-gerelateerde hepatotoxiciteit vergeleken met niet-zwangere vrouwen, het meest uitgesproken in het eerste trimester.

Hoofdstuk 7 beschrijft een foetaal-maternaal fysiologisch-gebaseerd farmacokinetisch model (f-m PBPK) dat gebruikt is om de overdracht van paracetamol door de placenta kwantitatief te voorspellen, en om de blootstelling aan paracetamol en de bijdragen van de specifieke metabolische klaringsroutes op de totale klaring in de volgroeide foetus te omschrijven. Verschillende benaderingen (ex-vivo cotyledon perfusie experimenten, schaling van placenta transfer via Caco-2 cel permeabiliteit en via fysisch-chemische eigenschappen [Mobi® default methode]) om

de placenta paracetamol overdracht in een PBPK model te integreren, werden geëvalueerd. De geteste placenta overdracht benaderingen toonden overeenstemmende uitkomsten in vergelijking met de geobserveerde PK. De ex-vivo cotyle-don benadering toonde de hoogste nauwkeurigheid om de concentratie te voorspellen. Blootstelling aan paracetamol in moederlijk veneus bloed was analoog aan die in foetale veneuze navelstrengbloed. De voorspelling van paracetamolklaring in de foetus geeft aan dat de mediaan dosisfractie van paracetamol omgezet naar paracetamol-sulfaat en NAPQI respectievelijk 0,8% en 0,06% waren.

Hoofdstuk 8 bevat een analyse van systematisch verkregen casuïstiek waarin het verband tussen maternaal paracetamol inname en foetale ductus arteriosus vernauwing of sluiting wordt beschreven. De *World Health Organization Uppsala Monitoring Centre* (WHO-UMC) causaliteitsbeoordeling werd toegepast om de casussen in perspectief te plaatsen en om de causaliteit te onderzoeken. Van de 25 beschreven casussen, werd in één enkel geval het verband geclassificeerd als onwaarschijnlijk, in negen gevallen als mogelijk, in elf als waarschijnlijk en in vier als zeker. Hieruit kan geconcludeerd worden dat een causale relatie tussen maternale paracetamol inname en foetale ductus arteriosus vernauwing of sluiting waarschijnlijk is. Daarom is farmacovigilantie van paracetamol tijdens de zwangerschap noodzakelijk om het werkelijk aantal gevallen te bepalen en om de huidige bevindingen in klinisch perspectief te plaatsen.

Sectie IV. Ouderen

Hoofdstuk 9 bevat een systematisch overzicht van de PK van paracetamol en veiligheidsdata in ouderen. Ouder worden gaf geen veranderingen in absorptie, maar wel een afname (3,9-22,9%) in Vd in fitte ouderen en zelfs een verdere afname van Vd (20,3%) in fragiele ouderen vergeleken met jongvolwassenen. De CL van paracetamol (29-45,7 en 37,5%) was eveneens lager in ouderen dan die in jongvolwassenen. Het was niet mogelijk om betrouwbare uitspraken te doen over de mogelijk veranderde veiligheid van paracetamol in ouderen. Dit hoofdstuk geeft inzicht in de resterende kennishiaten. Tevens worden aanbevelingen voor de toekomst verstrekt.

Hoofdstuk 10 beschrijft een populatie-PK model voor intraveneuze paracetamol in fitte ouderen. De CL en centrale Vd voor een ouder persoon met een lichaamsgewicht van 79 kg waren respectievelijk 17 L/uur en 54,9 L. Centrale Vd neemt exponentieel toe met lichaamsgewicht, terwijl de CL door geen enkele covariaat werd beïnvloed. Wanneer 10 mg/L werd gebruikt als target concentratie voor pijnstilling, onthulden de simulaties van gestandaardiseerde doseringsvoorschriften (1000 mg elke 6 uur of elke 8 uur) dat de gemiddelde oudere persoon de C_{ssmean} bereikte met 1000 mg elke 6 uur (9,2 mg/L), terwijl 1000 mg elke 8 uur resulteerde in een veel lagere C_{ssmean} (7,2 mg/L). Echter, vanwege een grote (onverklaarbare) variabiliteit in de PK van paracetamol, bereikte een aanzienlijk deel van de fitte ouderen niet de gewenste concentratie. In 90% van de populatie resulteert dit respectievelijk in een C_{ssmean} boven de 5,4 en 4,1 mg/L wanneer 1000 mg elke 6 uur of elke 8 uur wordt toegediend, en in 10% in een C_{ssmean} boven de 15,5 en 11,7 mg/L.

Hoofdstuk 11 beschrijft de PK van orale paracetamol en de variabiliteit in (fragiele) geriatrische gehospitaliseerde patiënten met behulp van populatie-PK modeleren. PK data werden het best beschreven met een 1-compartiment model. Ondanks de hoge interindividuele variabiliteit, werden er geen verklarende covariaten geïdentificeerd. Simulaties van 1000 mg elke 6 uur en elke 8 uur resulteerden respectievelijk in een C_{ssmean} van 10,8 mg/L [25-75ste percentielen 8,2-12,7] en 8,13 mg/L [6,3-9,6], voor de gemiddelde geriatrische gehospitaliseerde patiënt. De meerderheid van de populatie bereikte niet de gewenste concentratie ((22,2% (1000 mg q6h) en 52,2% (1000 mg q8h) < 8 mg/L; 31,3 (1000 mg q6h) en 7,6% (1000 mg q8h) > 12 mg/L)).

Sectie V. Algemene discussie

In **Hoofdstuk 12** wordt de *learn-confirm* cyclus gebruikt om te illustreren hoe de *evidence-based* doseringsvoorschriften in special populaties verkregen kunnen worden. De in deze thesis beschreven onderzoeken hebben als doel onze kennis betreffende de PK van paracetamol in special populaties te verbeteren. Inzicht in PK is de eerste benodigde stap, voordat de relatie tussen PK en PD kan worden onderzocht, om tenslotte te onderzoeken of doseringsaanpassingen in speciale populaties nodig zijn.
Allereerst wordt de huidige praktijk betreffende dosering in speciale populaties geïllustreerd. Vervolgens wordt de farmacometrische benadering (ontwerp, analyse en prospectieve klinische beoordeling) – de benadering die nodig is voor geïndividualiseerde dosering – en de implementatie van nieuwe doseringsvoorschriften besproken. In deze thesis worden, naast de reeds afgelegde weg, ook de stappen besproken die nodig zijn voor verdere optimalisatie van de *learn-confirm* cyclus van paracetamol in speciale populaties om te komen tot *evidence-based* doseringen. Vervolgens wordt zowel het belang om verder te kijken dan alleen naar paracetamol alsmede het gebruik van paracetamol als een voorbeeld geneesmiddel voor andere uridine 5'-diphosphoglucuronosyltransferase (UGT)1A1 substraten en als voorbeeld voor de ontwikkeling van de *learn-confirm* cyclus voor andere frequent gebruikte geneesmiddelen in special populaties benadrukt. Tenslotte worden aanbevelingen voor de toekomst gerelateerd aan de hierboven genoemde onderwerpen verstrekt.

Longgeneeskunde

Development of novel diagnostic approaches based
on pulmonary physiology
Applications in acute pulmonary embolism and obstructive sleep apnea

Dissertation

to obtain the degree of doctor at the University of Twente,
on the authority of the rector magnificus,
prof.dr. T.T.M. Palstra,
on account of the decision of the doctorate board,
to be publicly defended
on Friday the 21st of June 2019 at 14.45 hours

by

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Samenvatting

De belangrijkste functie van de longen is gasuitwisseling. De longen kunnen dit bereiken door een geraffineerde balans tussen ventilatie (welke het mogelijk maakt om verse, zuurstofrijke lucht te inhaleren en koolstofdioxide-rijke lucht weer uit te ademen) en perfusie (welke transport van zuurstof naar de organen en vice versa transport van koolstofdioxide mogelijk maakt). Een onbalans tussen ventilatie en perfusie van de longen kan desaturatie en hypercapnie veroorzaken. In het geval van acute longembolie (LE) is de perfusie aangedaan door een obstructie van (een deel van) de pulmonale vaten. In het geval van obstructief slaapapneu (OSA) is de ventilatie aangedaan door een (gedeeltelijke) obstructie van de bovenste luchtweg. Zowel LE als OSA delen nog een belangrijke eigenschap: in beide gevallen is een nieuwe diagnostische strategie gewenst.

Omdat LE een potentieel dodelijke ziekte is, moet het met hoge zekerheid uitgesloten zijn (indien aan LE gedacht wordt) voordat iemand ontslagen wordt uit het ziekenhuis (of diagnostiek naar overige pathologie ingezet wordt). Om dit te kunnen doen moet een computed tomography pulmonary angiography (CTPA)-scan verricht worden. De symptomen die zouden kunnen passen bij LE (voornamelijk kortademigheid en thoracale pijn) zijn echter aspecifiek. Daarom is het deel van de CTPA-scans waarop ook daadwerkelijk LE wordt aangetoond laag (ongeveer 25-30%). Dit leidt er toe dat er nieuwe strategieën nodig zijn om LE uit te kunnen sluiten om kosten en onnodige belasting van patiënten te voorkomen.

OSA gaat vaak gepaard met overmatige slaperigheid overdag en is geassocieerd met een verhoogd risico op cardiovasculaire problemen. De prevalentie van OSA stijgt snel (voornamelijk door de stijging in de prevalentie van obesitas). De diagnose van OSA vereist echter uitgebreide en dure testen, wat er toe leidt dat er een snelle stijging is in OSA-gerelateerde gezondheidszorgkosten en belasting van de slaapcentra. Desalniettemin lijdt een belangrijk deel van de mensen die verwezen worden vanwege verdenking op OSA niet aan deze aandoening (tot 30%). Daarom is er een behoefte aan goedkope, snelle, en valide mogelijkheden om OSA uit te sluiten. Het onderzoek dat in dit proefschrift gepresenteerd wordt, richt zich dan ook op de ontwikkeling van nieuwe diagnostische strategieën gebruikmakend van de ventilatie/perfusie onbalans bij LE (**hoofdstuk 2-4**) en OSA (**hoofdstuk 5-7**).

In **hoofdstuk 2** hebben we de diffusiecapaciteit van de longen voor stikstofmonoxide (TLNO) en koolstofmonoxide (TLCO) gemeten bij personen die verdacht werden van een LE en hebben we de ratio van deze diffusiecapaciteiten vergeleken met de resultaten van de CTPA-scans. De diffusiecapaciteit van de longen voor een bepaald gas is afhankelijk van een alveolair-capillaire membraan component (bijvoorbeeld een verdikt membraan zal leiden tot verminderde diffusie) en een hemodynamische component (bijvoorbeeld een afname in pulmonaal bloedvolume zal leiden tot verminderde diffusie). Door de hoge bindingsaffiniteit met hemoglobine is TLNO theoretisch vrijwel onafhankelijk van de hemodynamische component, terwijl TLCO ongeveer evenveel afhankelijk is van de membraan en hemodynamische component. De ratio van TLNO en TLCO zou daarom een indicatie moeten geven van de pulmonale hemodynamiek. De resultaten van onze studie die we presenteren in hoofdstuk 2 lieten geen verschillen zien in de TLNO / TLCO ratio tussen personen waarbij LE was aangetoond en personen waarbij LE was uitgesloten middels een CTPA-scan. Daarbij waren zowel TLNO als TLCO, gemiddeld genomen, verlaagd in zowel personen met als zonder LE. Deze afname werd waarschijnlijk (tenminste deels) veroorzaakt door een afname in alveolair volume. Dit afgenomen alveolair

volume kan op zijn beurt weer veroorzaakt zijn door de thoracale pijn (waar de meeste LE patiënten last van hebben,) welke kan leiden tot suboptimale inademing. Onze data leken er op te wijzen dat de TLNO/TLCO ratio niet gebruikt kan worden om LE uit te sluiten.

In **hoofdstuk 3** hebben we het gebruik van volumetrische capnografie om LE uit te sluiten op de spoedeisende hulp onderzocht. Onder normale fysiologische omstandigheden is de hoeveelheid koolstofdioxide in de uitgeademde lucht aan het eind van de uitademing ($PETCO_2$) ongeveer gelijk aan de hoeveelheid koolstofdioxide in het arteriële bloed ($PaCO_2$). LE geeft een verhoogde dode ruimte ventilatie (een deel van de longen wordt wel geventileerd maar niet doorbloed). In de delen zonder perfusie kan geen koolstofdioxide diffunderen naar de alveolaire lucht wat leidt tot een verlaagde hoeveelheid koolstofdioxide in de uitgeademde lucht. Vorige onderzoeken naar capnografie bij LE waren vooral gericht op het gebruik van (een combinatie van) $PETCO_2$ en $PaCO_2$. Volumetrische capnografie (het meten van de hoeveelheid koolstofdioxide in de uitademing als een functie van het uitgeademde volume) maakt het mogelijk om veel meer parameters te bepalen dan alleen $PETCO_2$. In hoofdstuk 3 hebben wij een nieuwe parameter ontwikkeld die verschillende volumetrische capnografie eigenschappen combineert. Deze nieuwe parameter was gedefinieerd als de per ademteug uitgeademde hoeveelheid koolstofdioxide (VCO_2) vermenigvuldigd met de helling van de alveolaire fase van het volumetrische capnogram (slopeIII), gedeeld door de ademfrequentie (RR) (dus $VCO_2 \times slopeIII/RR$). Zowel VCO_2 als slopeIII zullen waarschijnlijk verlaagd zijn bij LE terwijl de ademfrequentie waarschijnlijk toeneemt (om te compenseren voor de afname in VCO_2). Onze hypothese was dan ook dat onze nieuwe parameter verlaagd is bij personen met LE vergeleken met personen zonder LE. In het onderzoek dat we presenteren in hoofdstuk 3 hebben we volumetrische capnogrammen gemeten bij 30 personen die verdacht werden van LE, hebben we automatisch onze nieuwe parameter bepaald, en hebben we deze vergeleken met de CTPA-scans. In lijn met onze hypothese was de nieuwe parameter verlaagd bij personen waarbij LE bevestigd was vergeleken met personen waarbij LE uitgesloten was. De oppervlakte onder de receiver operating characteristic (ROC) curve van onze nieuwe parameter om LE uit te sluiten was 0.79 (95% betrouwbaarheidsinterval (BI) 0.64-0.95). Een waarde van de nieuwe parameter ≥ 1.90 Pa.min leek LE met hoge zekerheid uit te sluiten (sensitiviteit 100% (95%BI 77%-100%), negatief voorspellende waarde 100% (95%BI 68%-100%) en specificiteit 47% (95%BI 26%-69%). Door het kleine aantal geïncludeerde personen (en daarmee brede betrouwbaarheidsintervallen) was het nodig de nieuwe parameter (CapNoPE) te valideren.

In **hoofdstuk 4** voerden we een externe validatie van CapNoPE uit in een dataset van een eerdere studie naar volumetrische capnografie bij LE. In deze studie werd van 205 personen volumetrische capnogrammen verkregen. De diagnose LE werd gesteld met een CTPA-scan of met een bewezen diepe veneuze trombose gecombineerd met thoracale klachten. De resultaten in hoofdstuk 4 lieten zien dat CapNoPE opnieuw significant verlaagd was bij personen met LE vergeleken met personen zonder LE. De oppervlakte onder de ROC curve van CapNoPE om LE uit te sluiten was 0.71 (95%BI 0.64-0.79) en was in essentie gelijk aan de oppervlakte onder de ROC curves van meer conventionele capnografie parameters (zowel degenen waarin $PaCO_2$ gebruikt wordt als degenen zonder de noodzaak van $PaCO_2$). Desalniettemin was de diagnostische precisie van de afkapwaarde van ≥

1.90 Pa.min om LE uit te sluiten te laag om te gebruiken in de klinische praktijk (sensitiviteit 64.7% (95%BI 52.2%-75.9%), negatief voorspellende waarde 77.4% (95%BI 68.2%-84.9%) en specificiteit 59.9% (95%BI 51.1%-68.1%)).

In **hoofdstukken 5-7** hebben we diagnostische strategieën voor OSA onderzocht. De diagnose OSA is gebaseerd op de frequentie van apneus en hypopneus tijdens slaap, welke uitgedrukt wordt in de apneu-hypopneu-index (AHI). Volgens de huidige richtlijnen moet een hypopneu gepaard gaan met ofwel een wekreactie (arousal) ofwel een substantiële desaturatie (≥3% of ≥4% afhankelijk van de gebruikte definitie). Een volledige polysomnografie (PSG), waarbij onder andere slaap, ademhaling, respiratoire inzet (effort), desaturaties en arousals gemeten kunnen worden, wordt beschouwd als de gouden standaard diagnostische methode voor OSA. Het verrichten van een volledige PSG is echter duur en tijdsintensief. In ongecompliceerde gevallen is een polygrafie (PG), waarbij ademhaling, respiratoire inzet en desaturaties gemeten kunnen worden, voldoende. Hoewel een PG al een substantiële versimpeling van PSG is, zijn ook hieraan nog substantiële kosten verbonden en bovendien is het nog steeds noodzakelijk iedere registratie handmatig te beoordelen. Wij vermoedden dat het gebruik van oximetrie (mogelijk gecombineerd met een vragenlijst) een verdere versimpeling zou kunnen zijn die gebruikt kan worden om OSA uit te sluiten. Om dit vermoeden te staven, hebben we eerst de correlatie onderzocht tussen de AHI en de oxygen desaturation index (ODI, het aantal ≥3% desaturaties per uur) in PGs (**hoofdstuk 5**). Het specifieke doel was een afkapwaarde voor de ODI te identificeren en valideren waarmee OSA (gedefinieerd als een AHI ≥ 5) uitgesloten kon worden. Om dit te bereiken verdeelden we 3413 PGs in een training-set en een validatie-set. In de training-set bleek een ODI < 5 de beste voorspeller van een AHI < 5. In de validatie-set resulteerde dit in een sensitiviteit van 97.7% (95%BI 96.5% - 98.6%), een negatief voorspellende waarde van 91.4% (95%BI 87.1% - 94.6%) en een specificiteit van 97.0% (95%BI 93.8% - 98.8%). Vanwege de hoge diagnostische precisie van oximetrie in hoofdstuk 5, verrichtten we vervolgens een prospectieve studie naar het gebruik van automatisch beoordeelde oximetrie gecombineerd met de Philips vragenlijst bij 140 personen bij wie hun huisarts een OSA vermoedde (**hoofdstuk 6**). De Philips vragenlijst bestaat uit een combinatie van verschillende OSA-screenings vragenlijsten en is ontwikkeld in een populatie van werknemers van middelbare leeftijd. In het onderzoek dat we presenteren in hoofdstuk 6 onderzochten we de diagnostische precisie van twee vooraf gedefinieerde strategieën voor het verwijzen naar een slaapcentrum voor verdere diagnostiek naar OSA: 1) verwijs naar een slaapcentrum voor OSA diagnostiek als de ODI ≥ 5 is en 2) verwijs naar een slaapcentrum voor OSA diagnostiek als de ODI ≥ 5 is en/of de score op de Philips vragenlijst ≥ 55% is (welke wijst op een hoog risico op OSA). Deze strategieën werden vergeleken met de resultaten van de diagnostiek in de slaapcentra. Deze diagnostiek leidde niet tot een diagnose van OSA bij 40 van de 140 geïncludeerde personen (29%). De strategie om te verwijzen naar een slaapcentrum als de ODI ≥ 5 is, sloot OSA uit in 15% van de geïncludeerde personen en resulteerde in een sensitiviteit van 99.0% (95%BI 94.5% - 100.0%), een negatief voorspellende waarde van 95.2% (95%BI 76.2% - 99.9%), een specificiteit van 50.0% (95%BI 33.8% - 66.2%) en een positief voorspellende waarde van 83.2% (95%CI 75.2% - 89.4%). De tweetraps-strategie om te verwijzen naar een slaapcentrum als de ODI ≥ 5 is en/of de score op de Philips vragenlijst ≥ 55% is sloot OSA uit in 10% van de geïncludeerde personen en resulteerde in een sensitiviteit van 100.0% (95%BI 96.3% – 100.0%), een negatief voorspellende

waarde van 100.0% (95%BI 76.8% - 100.0%), een specificiteit van 35.0% (95%BI 20.6% - 51.7%) en een positief voorspellende waarde van 79.4% (95%BI 71.2% - 86.1%). Naast validatie van deze twee strategieën zochten we in de data ook naar een optimale strategie die het aantal verwijzingen nog verder zou kunnen doen dalen. Volgens deze exploratieve analyse kon een optimale diagnostische precisie worden bereikt als verwezen zou worden naar een slaapcentrum indien één van de volgende drie criteria aanwezig was: 1) de score op de Philips vragenlijst was ≥ 92%, of 2) de afgeronde ODI was ≥ 10, of 3) de afgeronde ODI was 5-10 én de score op de Philips vragenlijst was ≥ 46.5%. Deze strategie zou OSA uitgesloten hebben in 19% van de geïncludeerde personen en zou geresulteerd hebben in een sensitiviteit van 99.0% (95%BI 94.6% - 100.0%), een negatief voorspellende waarde van 96.3% (95%BI 81.0% - 99.9%), een specificiteit van 65.0% (95%BI 48.3% - 79.4%) en een positief voorspellende waarde van 87.6% (95%BI 80.1% - 93.1%). Concluderend, het gebruik van oximetrie met of zonder een vragenlijst maakte het betrouwbaar uitsluiten van OSA in de huisartsenpraktijk mogelijk. Het voordeel van de tweetraps-strategie is dat oximetrie alleen nodig zou zijn bij degenen met een laag of matig risico op OSA (dat wil zeggen, een score op de Philips vragenlijst < 55%). Aan de andere kant kon het aantal “onnodige” verwijzingen verder verlaagd worden met de strategie waarbij alleen oximetrie nodig is. De exploratieve analyse liet zelfs een strategie zien welke een nog hoger aantal personen zonder OSA zou kunnen identificeren maar deze strategie moet gevalideerd worden voordat zij in de klinische praktijk toegepast kan worden.

In **hoofdstuk 7** onderzochten we of analyse van uitgeademde lucht met een elektronische neus gebruikt kan worden om personen met OSA (gedefinieerd als een AHI ≥ 15) te herkennen in 83 personen die gepland stonden voor een PG vanwege verdenking op een OSA. Wij vermoedden dat de vele systemische (pathologische) processen die veroorzaakt worden door OSA weerspiegeld zouden kunnen worden in de uitgeademde lucht. De in hoofdstuk 7 gepresenteerde resultaten lieten zien dat één principale component (PC4) van de uitgeademde lucht data significant anders was in personen waarin OSA werd bevestigd vergeleken met personen waarin OSA werd uitgesloten. De precisie om personen met OSA te onderscheiden van personen zonder OSA was echter op zijn hoogst redelijk (cross-validation value 68.7%). PC4 kon wel gebruikt worden om de AHI als continue parameter te voorspellen (R^2=0.38). Door bekende OSA-gerelateerde factoren toe te voegen in een multivariaat model verbeterde de nauwkeurigheid van de voorspelling van de AHI substantieel (R^2=0.53). We waren ook geïnteresseerd in welke OSA-gerelateerde parameter het beste de uitademingsprofielen kon voorspelen. Hoewel hypoxie last (“hypoxic burden”) wel PC4 kon voorspellen bij univariate analyse (R^2=0.11), liet een multivariaat model zien dat alleen de AHI significant toegevoegde waarde had bij de voorspelling van PC4 (R^2=0.43). Dit suggereert dat de frequentie en niet de ernst van apneus en hypopneus tijdens slaap een grotere invloed heeft op processen die weerspiegeld worden in uitademingsprofielen. We concludeerden dat uitademingsprofielen niet gebruikt kunnen worden om OSA betrouwbaar uit te sluiten (als OSA gedefinieerd wordt als een AHI ≥ 15).

In **hoofdstuk 8** bespreken we de resultaten die we in hoofdstuk 2-7 presenteren en zetten we deze in perspectief. Een belangrijk onderwerp is de definities die gebruikt worden voor LE en OSA en de implicaties die ze zouden kunnen hebben op de resultaten.

Medical School Twente

Guidelines: Friend Or Foe?
Opportunities for Improvement of Cardiovascular Pharmacotherapy
Based on Evidence From Real-World Observational Data

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Twente,
op gezag van de rector magnificus,
prof. dr. T.T.M. Palstra,
volgens besluit van het College voor Promoties
in het openbaar te verdedigen
op woensdag 29 mei 2019 om 14.45 uur

door

Wilhelmina Joanneke Kruik-Kollöffel
geboren op 5 april 1965
te Utrecht

Promotor:	prof. dr. J.A.M. van der Palen
Copromotoren:	dr. G.C.M. Linssen
	dr. K.L.L. Movig

Samenvatting

Richtlijnen die het keuzeproces in de dagelijkse patiëntenzorg ondersteunen zijn noodzakelijk om de stijgende aantallen publicaties met resultaten uit klinische onderzoek het hoofd te kunnen bieden. De hoeveelheid bewijs die voortkomt uit klinisch onderzoek is eenvoudigweg te veel om door een individuele professional in de gezondheidszorg te kunnen beheersen. In de gezondheidszorg spelen richtlijnen een belangrijke rol in de medicamenteuze behandeling van patiënten. Richtlijnen kunnen, precies zoals het woord al aangeeft, richting geven aan de behandeling van patiënten. Aan de andere kant kunnen richtlijnen aanvoelen als een te strak keurslijf, een harnas, dat de professionele vrijheid belemmert. Zodra richtlijnen gebruikt worden om een individuele professional in de gezondheidszorg terecht te wijzen omdat deze niet "op het rechte pad" blijft, worden richtlijnen een vijand in plaats van een vriend. In de algemene introductie van dit proefschrift (**Hoofdstuk 1**) beschreven we dit delicate evenwicht. Tevens beschreven we de vooren nadelen van "real-world data" en "real-world evidence": het verzamelen van data uit "de echte wereld", als tegenovergestelde van data uit klinisch onderzoek, en bewijs dat daaruit voortkomt. Deze twee thema's, richtlijnen en "real-world evidence" op basis van "real-world data", vormden het startpunt van dit proefschrift.

In **Hoofdstuk 2 en 3** onderzochten we het verband tussen voorschrijfgedrag van maagbeschermende medicatie en officiële berichtgevingen betreffende de interactie tussen clopidogrel en protonpompremmers. Na de eerste berichtgeving van registratie-autoriteiten in juni 2009, om de combinatie van clopidogrel en protonpompremmer te vermijden, vonden we een sterke toename van het gebruik van H2-antagonisten zowel in nieuwe gebruikers, met een piek tot 25% van deze gebruikers, als in patiënten die voorheen al maagbeschermende middelen gebruikten. Aangezien H2-antagonisten minder effectieve maagbeschermende middelen zijn, lopen deze patiënten een risico op maagbloedingen en in mindere mate bloedingen in de darm. Deze toename in het voorschrijven van H2-antagonisten verdween na enige maanden. In februari 2010 werd een aangepaste berichtgeving gepubliceerd waarin geadviseerd werd om alleen de combinatie met (es)omeprazol te vermijden. Hierop toonden we bij nieuwe gebruikers van maagbeschermende middelen een daling van bijna 12% aan voor (es)omeprazol en een toename van 16% voor andere protonpompremmers. Echter, nog steeds startte 22.6% van de patiënten met (es)omeprazol, waardoor deze patiënten werden blootgesteld aan een theoretisch risico op een verminderde effectiviteit van clopidogrel. Dezelfde trends konden worden aangetoond in patiënten die reeds maagbeschermende medicatie gebruikten, hoewel minder uitgesproken, zoals te verwachten, aangezien bij deze patiënten de maagbeschermende medicatie aangepast zou moeten worden bij de start van clopidogrel. Een medicatiewijziging vormt immers een risico op verminderde therapietrouw. Het feit dat men de officiële berichtgevingen slechts in beperkte mate opvolgde kan veroorzaakt zijn door het twijfelachtige wetenschappelijke bewijs voor deze veronderstelde interactie.

In **Hoofdstuk 4** onderzochten we in welke mate de Europese richtlijnen voor hartfalen hebben geleid tot het voorschrijven van evidence-based medicatie in een grote groep patiënten bij ontslag na een eerste ziekenhuisopname voor hartfalen. Wij onderzochten dit Nederlandse cohort met behulp van een grote PHARMO database tussen 2001 en 2015, een periode waarin grote voortgang werd geboekt in de behandeling van hartfalen. Het nakomen van de richtlijnen

verschilde per aanbeveling. Opvallend was de afwezigheid van een significante toename in het voorschrijven van mineralocorticoïde-receptor antagonisten. Tegelijkertijd toonden wij ontwikkelingen aan die niet in de richtlijnen stonden, bijvoorbeeld de verschuiving van angiotensine-converting-enzym remmers naar angiotensinereceptorblokkers. Hoewel de hartfalenclassificatie van onze patiënten onbekend was, verschaffen onze data, uitgaande van een relatief stabiele case-mix, inzicht in "real-world" medicamenteuze behandeling van patiënten na een ziekenhuisopname voor hartfalen. Inzicht in de implementatie van huidige richtlijnen kan helpen om de implementatie van toekomstige richtlijnen te verbeteren.
Een opname voor hartfalen markeert een verslechtering van de prognose en patiënten na een eerste ziekenhuisopname voor hartfalen hebben een groot risico op een heropname voor hartfalen. In de **Hoofdstukken 5, 6 en 7** onderzochten we de associatie tussen medicatie voorgeschreven bij ontslag en het risico op een heropname voor hartfalen in een "real-world", grote, niet geselecteerde patiëntengroep.

Allereerst werden in **Hoofdstuk 5** de groepen geneesmiddelen onderzocht die de kern vormen voor de behandeling van hartfalen: diuretica, bètablokkers, angiotensine-converting-enzymremmers/angiotensinereceptorblokkers en mineralocorticoïde-receptor antagonisten. Het bewijs voor het gebruik van deze klassen van hartfalenmiddelen is geleverd door grote gerandomiseerde klinische trials. In ons "real-world" cohort, lieten carvedilol (een bètablokker), mineralocorticoïde-receptor antagonisten en diuretica een verhoogde kans zien op een heropname, respectievelijk met een factor 1.25, 1.09 en 1.14. Alleen het voorschrijven van selectieve bètablokkers met een registratie voor hartfalen (bisoprolol, metoprolol en nebivolol) resulteerde in een verlaagde kans op heropname met een hazard ratio van 0.94. Alle risico's werden gecorrigeerd voor comorbiditeiten door gebruik te maken van propensity scores. Op basis van onze resultaten zou een selectieve bètablokker de voorkeur hebben boven de niet-selectieve bètablokker carvedilol. De keuze voor angiotensine-converting-enzym remmers of angiotensinereceptorblokkers lijkt te passen bij de respectievelijke patiëntprofielen.

In **Hoofdstuk 6** werd de associatie onderzocht tussen een heropname voor hartfalen en de additionele hartfalenmiddelen en de cardiovasculaire middelen die niet bij hartfalen worden toegepast. Volgens het behandelschema in de richtlijnen kan digoxine worden voorgeschreven aan geselecteerde patiënten, bovenop de geneesmiddelen die de kern vormen van de hartfalenbehandeling. Op basis van onze resultaten zou gesteld kunnen worden dat het klinische belang van digoxine wordt onderschat, omdat het risico op heropnames een factor 0.93 lager was in gebruikers ten opzichte van niet-gebruikers. Kijkend naar het lagere risico op heropname voor hartfalen, zou acetylsalicylzuur monotherapie (hazard ratio 0.90) de voorkeur moeten krijgen boven monotherapie met een P2Y12-remmer(hazardratio 1.26). Dit is in het bijzonder interessant, omdat sinds 2013-2014 monotherapie met clopidogrel (een P2Y12-remmer), meer en meer wordt gebruikt in plaats van acetylsalicylzuur (met of zonder dipyridamol) als secundaire profylaxe bij cerebrovasculaire incidenten. Het risico voor een heropname was verhoogd voor patiënten die statines (hazard ratio 1.21), nitraten (hazard ratio 1.18) of amiodaron (hazard ratio 1.31) gebruikten. Het verhoogde risico op een heropname

voor deze middelen kan mogelijk verklaard worden door de comorbiditeiten waarvoor deze middelen worden voorgeschreven.
De medicamenteuze behandeling van comorbiditeiten kan het risico op een heropname voor hartfalen beïnvloeden.

In **Hoofdstuk 7** presenteerden we een hypothese-genererende studie waarin we de associatie tussen niet-cardiovasculaire medicatie en de kans op een heropname voor hartfalen onderzochten. In sommige gevallen bleek de associatie met heropname in overeenstemming met wat we al weten. Echter, ook enkele onverwachte bevindingen werden gedaan, zoals de afwezigheid van een associatie tussen het gebruik van niet-steroïdale anti-inflammatoire geneesmiddelen (NSAID's) en heropname. De verschillende sulfonylureumderivaten laten een verschillend effect zien op het risico op heropname voor hartfalen, niet altijd in overeenstemming met het bestaande bewijs. Hartfalenpatiënten aan wie middelen tegen jicht zijn voorgeschreven hebben een verhoogd risico op een heropname en dienen daarom intensiever bewaakt te worden, onafhankelijk van de vraag of het gebruik van deze medicatie een kenmerk is van de ernst van de ziekte, of een echte risicofactor. Het gebruik van insuline was geassocieerd met een verhoogd risico op heropname ten opzichte van patiënten die geen insuline gebruiken. Echter, het heropnamerisico van insuline was niet toegenomen bij hartfalenpatiënten met diabetes type 2 in vergelijking met patiënten die alleen andere bloedsuikerverlagende middelen gebruiken. Hoewel interne en externe validatie de statistische robuustheid van het model aantoonden, dienen onze resultaten als hypothese-genererend te worden beschouwd.

Het bewijs dat we verzameld hebben in onze 2 grote patiënten cohorten, respectievelijk 39.496 en 22.476 patiënten, probeerden we in de algemene discussie (**Hoofdstuk 8**) te vertalen naar een individuele, fictieve patiënt, genaamd John. De toegevoegde waarde van de ziekenhuisapotheker voor cardiovasculaire patiënten wordt hier eveneens beschreven.

Neurologie

Secondary intestinal motility disorders: clues for a better diagnosis

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Twente,
op gezag van de rector magnificus,
prof. dr. T.T.M. Palstra,
volgens besluit van het College voor Promoties
in het openbaar te verdedigen
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door

Marjanne den Braber-Ymker
geboren op 6 mei 1986
te Zweeloo, Nederland

Promotoren: prof. dr. ir. M.J.A.M. van Putten
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Samenvatting
Darmmotiliteit wordt gereguleerd door het enterische zenuwstelsel (Engels: enteric nervous system, ENS), de interstitiële cellen van Cajal (ICC's) en de gladde spiercellen van de muscularis propria. Afwijkingen in een of meer van deze structuren kunnen leiden tot een verstoring van de darmmotiliteit, samengevat onder de noemer gastro-intestinale neuromusculaire ziekte (GINMD). De term GINMD omvat een klinische heterogene groep van zowel primaire motiliteitsstoornissen, waarbij het neuromusculaire systeem van de darm primair is aangedaan (bijvoorbeeld ziekte van Hirschsprung of chronische intestinale pseudo-obstructie), als secundaire motiliteitsstoornissen, die het gevolg zijn van een systemische ziekte (bijvoorbeeld systemische sclerose of amyloïdose). Primaire GINMD's zoals chronische intestinale pseudo-obstructie of slow-transit obstipatie tonen een grote individuele variatie, waarbij een breed spectrum aan histologische kenmerken in de darm wordt gezien. Hierdoor is het onmogelijk om één algemeen onderliggend pathofysiologisch mechanisme te onderscheiden. De etiologie van secundaire GINMD's is over het algemeen duidelijker, maar de histopathologische kenmerken zijn meestal niet systematisch onderzocht.
In dit proefschrift wordt de histologische achtergrond van de pathofysiologie van secundaire motiliteitsstoornissen met een duidelijke etiologie (beschadiging van het ruggenmerg, amyloïdose en systemische sclerose) onderzocht om mogelijke mechanismen van darmmotiliteitsstoornissen te begrijpen.

Deel I: Methodologische issues
Het myenterische netwerk van ICC's heeft een belangrijke rol in de peristaltiek en zorgt onder andere voor de voortplanting van 'slow waves' naar de gladde spiercellen. Verlies van ICC's kan daarom leiden tot dismotiliteit van de darm. De Internationale Werkgroep voor GINMD beschrijft in haar richtlijnen het belang van histologische beoordeling van ICC's in de darm voor de diagnose van patiënten met GINMD. Het aantal ICC's kan op een kwantitatieve manier worden bepaald, waarbij het vermelden van een afname met meer dan 50% nuttig kan zijn in de diagnostiek. De kwantitatieve methoden die in de literatuur worden gebruikt zijn echter momenteel niet praktisch voor de dagelijkse routine van de patholoog. Daarom presenteerden we in **hoofdstuk 2** een eenvoudige semikwantitatieve methode om de ICC's in de myenterische plexus van de darm te schatten. In deze studie werden twee controlegroepen en vier groepen bestaande uit patiënten met gastro-intestinale motiliteitsstoornissen gevormd. De voorgestelde schattingsmethode voor het myenterische ICC-netwerk toonde over het algemeen een goede interobserver- en intra-observerovereenkomst en een goede betrouwbaarheid. Er werden meer myenterische ICC's gevonden in de dunne darm dan in de dikke darm. Tussen verschillende regio's in het colon werden geen significante verschillen gevonden. Er waren ook geen verschillen tussen de oriëntatie van de coupes (dwars- of lengtedoorsnede van de darm). Aangezien de beschreven methode eenvoudig en semikwantitatief in staat is om onderscheid te maken tussen normaal en ziek weefsel, kan deze worden gebruikt bij routinematige diagnostiek van GINMD.

Hoofdstuk 3 beschrijft op welke semikwantitatieve manier het aantal neuronen, de dichtheid van het zenuwvezelnetwerk (inclusief gliacellen) en het gladde spierweefsel in de muscularis propria zijn geëvalueerd. Deze methoden zijn gebruikt in de studies in de hoofdstukken 3 tot en met 5.

Deel II: Secundaire motiliteitsstoornissen

Een schematisch overzicht van de belangrijkste histologische bevindingen bij beschadiging van het ruggenmerg, amyloïdose en systemische sclerose wordt gegeven in Figuur 7.1.

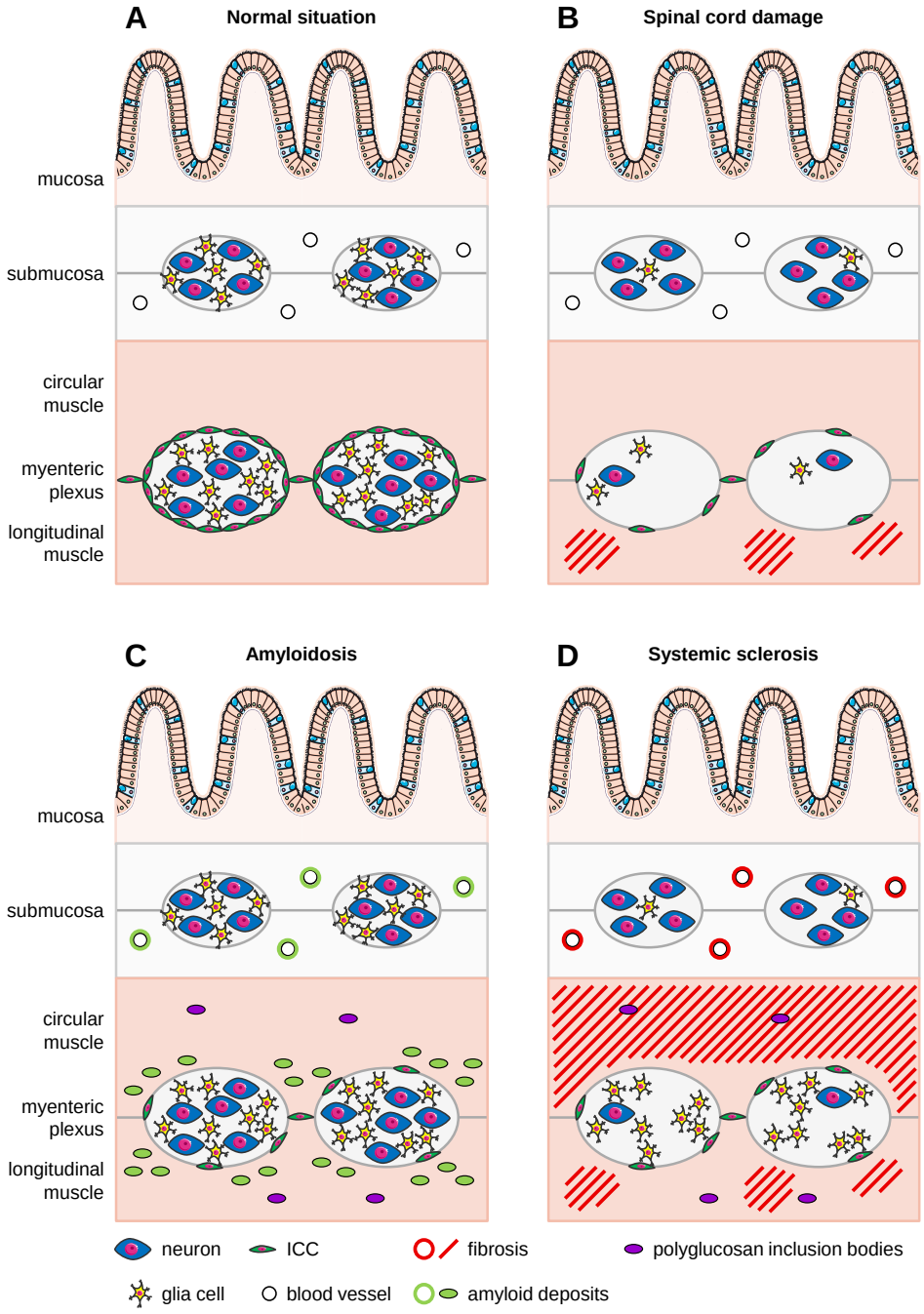

Figure 7.1 Graphic summary of the main histological findings in secondary motility disorders. A) Schematic representation of the gut wall in normal condition. Only structures studied in this thesis are shown: submucosal and myenteric plexuses, myenteric ICC network, muscularis propria and blood vessels. B) Major histological changes in spinal cord damage were decreased neurons in the myenteric plexus (colon), loss of glial cells, fibrosis in the longitudinal muscle layer and reduction of the myenteric ICC network. C) In amyloidosis, amyloid deposits were found in the vascular walls (AL and AA patients) and in the muscularis propria (AL patients). Polyglucosan inclusion bodies were present in the muscularis propria, and a reduction of ICCs was shown. D) Findings in systemic sclerosis were fibrosis in the blood vessel walls, and in the circular and longitudinal muscle layers. Neurons were decreased in the myenteric plexus (colon), loss of glial cells were shown in the submucosal plexus, polyglucosan inclusion bodies were present in the muscularis propria, and the ICC network was reduced. ICC, interstitial cell of Cajal. This figure is created with images adapted from Servier Medical Art (Intestinal villi; Neuron). Original images are licensed under a Creative Commons Attribution 3.0 Unreported License. Simplification and colour changes were made to the original neuron and mucosa cartoons.

Beschadiging van het ruggenmerg

Spina bifida en dwarslaesie zijn aandoeningen waarbij het ruggenmerg beschadigd is. Dit resulteert in een onderbreking van de extrinsieke zenuwvezels van de darminnervatie. Voor een goede darmmotiliteit is zowel intrinsieke innervatie (ENS) als extrinsieke innervatie nodig. De intrinsieke peristaltische reflex wordt gemoduleerd door extrinsieke zenuwvezels. Beschadiging van deze extrinsieke input kan daarom resulteren in dismotiliteit van de darm. In de dikke darm kan dit leiden tot obstipatie.

In **hoofdstuk 4** hebben we dikke darmweefsel van patiënten met spina bifida en dwarslaesie onderzocht. We hebben onderscheid gemaakt tussen een groep met ernstige motiliteitsstoornissen (als indicatie voor de operatie) en een groep met lichte of zonder motiliteitsstoornissen (andere indicaties voor chirurgie, informatie over andere symptomen gerelateerd aan dismotiliteit was niet beschikbaar).
In deze patiëntengroepen verwachtten we veranderingen in het ENS, voornamelijk veranderingen in de dichtheid van neuronen en/of gliacellen. In onze studie werd vooral afname van het myenterische ICC-netwerk gevonden bij bijna alle spina bifida en dwarslaesie patiënten, maar slechts een vermindering van de dichtheid van neuronen bij ongeveer tweederde van deze patiënten. Het ICC-netwerk zou daarom de eerste structuur van het neuromusculaire apparaat kunnen zijn die wordt aangedaan als gevolg van beschadigde extrinsieke innervatie. Vervolgens zou de afname van ICC's kunnen resulteren in een verlies van neuronen en gliacellen in de myenterische plexus. Daarnaast zagen we bij patiënten met ernstige motiliteitsproblemen een significante afname van enterische gliacellen. Dit kan wijzen op de relevante rol die gliacellen spelen bij de regulatie van motiliteit, zoals beschreven in de literatuur. Er konden geen verschillen worden gevonden tussen patiënten met spina bifida (aangeboren ziekte) en dwarslaesie (verworven ziekte), wat suggereert dat veranderingen in het neuromusculaire apparaat een gevolg zijn van verstoorde extrinsieke innervatie onafhankelijk van etiologie.

Amyloïdose
Amyloïdose omvat een diverse groep stapelingsziekten van verkeerd gevouwen eiwitten (amyloïd) in verschillende weefsels.
In **hoofdstuk 5** bestudeerden we darmweefsel van patiënten met AL- en AA-amyloïdose, de twee meest voorkomende soorten amyloïdose. AL-amyloïdose is het gevolg van groei van plasmacellen in het beenmerg dat resulteert in een hoge productie van immunoglobulines. De onderliggende ziekten van AA-amyloïdose zijn chronische ontstekings- of infectieziekten (zoals reumatoïde artritis en de ziekte van Crohn). Hierdoor wordt een verhoogd niveau van het ontstekingseiwit serum amyloïd A geproduceerd door de lever. Zowel bij AL als bij AA-amyloïdose kunnen onoplosbare eiwitten in allerlei inwendige organen neerslaan als amyloïd, waaronder het maagdarmkanaal.
In de literatuur wordt beschreven dat verschillende mechanismen verantwoordelijk zijn voor intestinale pseudo-obstructie bij amyloïdosepatiënten: een enterische myopathie in AL-amyloïdose en een neuropathie in AA-amyloïdose. Daarnaast worden amyloïdafzettingen vaak aangetroffen in de vaatwanden van beide typen amyloïdose, wat kan leiden tot ischemie en verdere beschadiging van neuromusculaire structuren in de darmwand. We verwachtten daarom spierveranderingen in AL-amyloïdose, neurale veranderingen in AA-amyloïdose en amyloïdneerslag in bloedvaten bij beide typen amyloïdose. In het slijmvlies waren amyloïdafzettingen aanwezig in AA-patiënten maar afwezig in AL-patiënten. Depositie van amyloïd was aanwezig in de vaatwanden van alle patiënten zoals we hadden verwacht. Er werden geen verschillen gevonden tussen de AL- en AA-amyloïdosegroepen in de spierlagen en zenuwplexussen van de darmwand. Op basis van onze histologische bevindingen, hebben we een alternatieve hypothese voorgesteld over het proces van intestinale dismotiliteit bij amyloïdose: Amyloïdafzetting vindt als eerste plaats in de bloedvatwanden. Daarna slaat het amyloïd neer in de muscularis propria. Dit kan vervolgens van invloed zijn op het functioneren van het myenterische ICC-netwerk, leidend tot ICC-verlies. Ten slotte kan de myenterische plexus betrokken raken, wat zou kunnen resulteren in klinische symptomen van ernstige dismotiliteit (bijv. pseudo-obstructie).

Systemische sclerose
In **hoofdstuk 6** hebben we histologische kenmerken van verminderde darmmotiliteit bij systemische sclerose (SSc) onderzocht. SSc is een complexe bindweefselaandoening waarvan de oorzaak onbekend is. De ziekte resulteert in ophoping van collageen in de huid en viscerale organen, inclusief het maagdarmkanaal. Verschillende processen spelen een rol bij de pathogenese van SSc: een afwijkend immuunsysteem leidt tot de productie van auto-antilichamen en auto-immuniteit, microvasculopathie en disfunctionerende fibroblasten wat leidt tot overmatige fibrose. Als de darmen zijn aangedaan kan dit leiden tot verminderde motiliteit. Processen die betrokken zijn bij de pathogenese in de darmen zijn microvasculaire schade, disfunctie van autonome zenuwen, musculaire atrofie en fibrose, en auto-antilichamen. Momenteel is het niet duidelijk hoe deze mechanismen op elkaar inwerken. Waarschijnlijk zijn microvasculaire schade en ischemie de belangrijkste gebeurtenissen bij betrokkenheid van de darmen.
In de literatuur wordt beschreven dat ontwikkeling van intestinale dismotiliteit bij SSc een sequentieel proces zou kunnen zijn. Dit proces zou beginnen met vasculaire veranderingen, leidend tot neurale schade, atrofie van de muscularis propria en gevolgd door fibrose. Daarom verwachtten we dat in weefselmateriaal van SSc-

patiënten met fibrose in de muscularis propria (het eindstadium van het proces van intestinale dismotiliteit) tevens vasculaire veranderingen en neurale schade waargenomen zou kunnen worden. Onze resultaten konden dit slechts gedeeltelijk bevestigen, wat suggereert dat in plaats van sequentiële veranderingen, meerdere parallelle processen plaatsvinden. Deze verschillende processen zouden de grote variatie in morfologische kenmerken en klinische klachten tussen individuele patiënten kunnen verklaren.

Algemene conclusie

Tot slot worden de resultaten en conclusies van dit proefschrift in een breder perspectief besproken. De twee opvallendste bevindingen in onze studies naar secundaire motiliteitsstoornissen zijn een afgenomen dichtheid van het myenterische ICC-netwerk en een verminderde dichtheid van gliacellen in een groot deel van de patiëntgroepen. Door ons te beperken tot goed gedefinieerde secundaire motiliteitsstoornissen hebben we gestreefd naar zo uniform mogelijke groepen, in tegenstelling tot de heterogene groep van primaire GINMD's. De studie naar specifieke ziektebeelden heeft nieuwe inzichten en hypotheses binnen het veld van de GINMD's opgeleverd. De verrassende heterogeniteit binnen onze patiëntencohorten maakt het niet goed mogelijk om algemene pathofysiologische mechanismes af te leiden voor (primaire) darmmotiliteitsstoornissen. In de toekomst zal het daarom belangrijk blijven om de neuromusculaire structuren in de darm van elke individuele patiënt met ernstige klinische motiliteitsklachten te beoordelen. Een zorgvuldige histopathologische diagnose zal uiteindelijk bijdragen aan een nauwkeurige diagnose, een betere prognose en beter aansluitende (gerichte) therapie voor de patiënt.

Reumatologie

Stopping Tumor Necrosis Factor Inhibitors in Well Controlled Rheumatoid Arthritis Patients: The Poet Study

Proefschrift

ter verkrijging van de graag van doctor aan de Universiteit Twente.
op gezag van de rector magnificus prof. dr. T.T.M. Palstra,
volgens besluit van het College voor Promoties
in het openbaar te verdedigen
op vrijdag 22 maart 2019 om 16:45 uur

door

Marjan Ghiti Moghadam
geboren op 3 juli 1969
te Tehran- Iran

Promotor: Prof. dr. M.A.F.J. van de Laar
Copromotoren: Dr. H.E. Vonkeman
Dr. T.L.C.M. Jansen

Samenvatting en algemene beschouwing

Rond de eeuwwisseling begon de behandeling van Reumatoïde Artritis (RA) te veranderen van zorgen voor de patiënten naar een situatie waarin genezing een reële optie is geworden voor patiënten. De basis voor deze verandering was de ontwikkeling en introductie van remmers van Tumor Necrosis Factor (TNFi) en later andere therapeutische aangrijpingspunten. Achteraf gezien blijkt de effectiviteit van deze nieuwe klasse van geneesmiddelen. in het algemeen biologicals genoemd. beter dan verwacht. waardoor de prognose en het perspectief van veel RA patiënten en patiënten die lijden aan andere auto-immuunziekten verbeterde. Tijdens de ontwikkeling en introductie van TNFi was de aandacht begrijpelijk, vooral gefocust op effectiviteit en veiligheid na start van de behandeling. Verlaging van de dosis, of stoppen van de behandeling. in geval van gunstige behandelresultaten kreeg nauwelijks aandacht of werd niet overwogen. De veronderstelling dat auto-immuunziekten zoals RA chronische ziekten zijn. die levenslang behandeld dienen te worden, en in het beste geval slechts progressie kan worden afgeremd. bleef de leidende gedachte van zowel professionals als patiënten.

We werden voor het eerst geconfronteerd met de noodzaak om behandeling met TNFi te stoppen of te onderbreken toen het weliswaar verwachte toegenomen risico op infectie realiteit bleek te zijn. Richtlijnen om het infectierisico als gevolg van remming van TNF te verminderen werden ontwikkeld en succesvol geïmplementeerd. Hoewel nauwelijks onderzocht. bestond de indruk bij behandelaars dat na stoppen van TNFi in verband met infectie or verhoogd infectierisico (met name geplande operaties), toename van ziekteactiviteit voorkomt. maar dat hervatten van de behandeling leidde tot snelle herwonnen respons.

Studies naar het induceren van remissie later meestal “treating to the target of remission" (T2T) genoemd, was een direct gevolg van de indrukwekkende klinische effecten van de introductie van biologicals. Het hoge percentage RA patiënten in studies in de dagelijkse praktijk bij wie stabiele remissie kon worden bereikt door gebruik te maken van de therapeutische mogelijkheden, in combinatie met de toegenomen geneesmiddelkosten en zorgen over levenslange behandeling. bereidde de weg voor studies naar dosisverlaging of stoppen van TNFi in geval van goede klinische effecten (remissie of lage ziekte activiteit). Hoewel wetenschappelijke argumenten tegen dosisverlaging, met name immunogeniciteit, sterker zijn dan de argumenten tegen meteen stoppen, zijn met name psychologische argumenten van patiënten en behandelaars de oorzaak dat de meerderheid van de gedane studies de focus hebben gelegd op dosisverlaging. De meeste studies werden gestart op initiatief van de onderzoeker en daarom begrijpelijk van geringe omvang en onderhevig aan methodologische beperkingen. De POEET studie, de basis voor dit proefschrift, was een gecombineerd initiatief van Nederlandse reumatologen en zorgbeleidmakers. Deze gezamenlijke Nederlandse inspanning heeft geresulteerd in een van de grootste studies naar doelmatig gebruik van biologicals in RA, in dit geval door te stoppen. Hoewel ook deze studie beperkingen kent, zoals het open-label en pragmatische studieontwerp, maakt het indrukwekkende aantal deelnemende patiënten het mogelijk niet alleen de hoofdvraag van de studie maar ook extra onderzoeksvragen. zoals de betrokken mechanismen en de invloed op patiënten en de maatschappij, te onderzoeken.

In het eerste hoofdstuk van dit proefschrift heb ik bestaande informatie over stoppen en afbouwen van biologicals voor RA besproken in combinatie met een theoretisch schema voor de mogelijk onderliggende mechanismes.

Hoofdstuk 2

Dit hoofdstuk is de eerste en meeste belangrijke publicatie van de POEET studie. Het was mijn eer om, namens het POEET team, te laten zien dat stoppen van TNFi mogelijk was bij 48% van RA patiënten in stabiele remissie of lage ziekteactiviteit (LDA). Maar de stopstrategie resulteerde wel in een meer dan drievoudig toegenomen kans op klachten en verschijnselen van toegenomen ziekteactiviteit (exacerbatie) binnen 12 maanden ten opzichte van RA patiënten die hun TNFi bleven gebruiken. We hebben ook laten zien dat de gemiddelde ziekteactiviteit in de stopgroep significant verhoogd was gedurende de observatieperiode, maar in de meeste patiënten bleef de ziekteactiviteit onder de grens van matige activiteit. Omdat verschillende definities van exacerbatie in de literatuur gebruikt worden, hebben we sensitiviteitsanalyses uitgevoerd met verschillende definities, hetgeen vergelijkbare resultaten aantoonde. De resultaten van onze studie bevestigen in grote lijnen de bevindingen van eerdere, veelal kleinere studies.

Eerdere TNFi stop studies in RA lieten een brede spreiding (18-88%) zien van het risico op exacerbatie van ziekteactiviteit. De verschillen in deze resultaten kunnen onder andere verklaard worden door de heterogeniteit van de RA populaties, verschillende definities van exacerbatie, (rest) ziekteactiviteit bij inclusie en het parallel gebruik van andere DMARDs. Gerandomiseerde studies naar het stoppen van specifieke TNFi's rapporteerden ook verschillende resultaten. De Amerikaanse “Corrona registry" studie rapporteerde dat ruim 70% van de RA patiënten gedurende 12 maanden observatie na het stoppen van een eerste TNFI geen exacerbatie meemaakten. De EMPIRE trial, PRESERVE trial, en DOSERA studies meldden dat respectievelijk ongeveer 57%, 43% en 13% van de RA patiënten succesvol konden stoppen met etanercept tijdens de studie. De OPTIMA trial, HONOR en BRIGHT studies rapporteerden dat respectievelijk 56%, 58% en 18% van de RA patiënten in remissie of lage ziekteactiviteit bleven na stoppen van hun TNFï. Het stoppen van infliximab werd beschreven in de studie van Quinn et al., de BeSt studie en de “Remission induction by Remicade in RA” (RRR.studie). De studies rapporteerden blijvende lage ziekteactiviteit of remissie in respectievelijk 70%, 25% en 50% van de patiënten. Als laatste rapporteerde een kleine studie over stoppen van certolizumab-pegol, in tegenstelling tot de hiervoor genoemde studies, geen positief resultaat.

In onze POEET studie werd, in geval van exacerbatie na stoppen van TNFi, geadviseerd de TNFi te hervatten. De geobserveerde data laten zien dat herbehandeling resulteerde in succes bij de meeste patiënten (83.1% succes na hervatten TNFi) in de meeste gevallen binnen 12 weken. Aanvullend werden er geen (ernstige) negatieve gebeurtenissen geobserveerd na hervatten van TNFi. Tenslotte hebben we geobserveerd dat in de stopgroep ten opzichte van de continueergroep meer ziekenhuisopnames plaatsvonden, weliswaar volgens de behandelaar niet gerelateerd aan het stoppen. De redenen voor opname in een ziekenhuis waren: infecties. geplande operaties, maligniteiten en fracturen. We zijn tot de conclusie gekomen dat het stoppen van TNFi bij RA patiënten en hervatten van TNFI in geval van exacerbatie veilig lijkt te zijn.

In aanvulling op het stoppen van TNFi zijn er meerdere strategieën denkbaar voor verlaging van de dosis. Vanzelfsprekend overschrijdt de variabiliteit hiervoor de opties voor onmiddellijk stoppen. zoals werd gedaan in de POEET studie. De PRESERVA, DOSERA en DRESS studies gebruikten een verschillende afbouwstrategie ten opzichte van de STRASS en de RETRO studie. In het algemeen lieten deze studies zien dat minder exacerbaties optraden tijdens dosisverlagingen in vergelijking met stoppen, maar op langere termijn zijn de resultaten van dosisreductieschema's en

meteen stoppen vergelijkbaar. Het risico op exacerbatie tijdens dosisreductie is lager dan dat tijdens meteen stoppen, maar het cumulatieve risico van alle sequentiële dosisverlagingen is goed vergelijkbaar met het risico op exacerbaties na volledig stoppen. Recent liet de DRESS studie zien dat ziekteactiviteit-gestuurd dosis verlagen van adalimumab en etanercept “non-inferior” is met betrekking tot ernstige exacerbaties ten opzichte van doorgaan van de medicatie.

Hoofdstuk 3

In dit hoofdstuk gingen we op zoek naar voorspellers voor het succesvol (niet resulterend in een exacerbatie van ziekteactiviteit) stoppen van TNFi. Dit hoofdstuk helpt de theorie zoals beschreven in hoofdstuk 1 te begrijpen en verder te vormen. Onze analyse liet zien dat 70% van de RA patiënten in stabiele remissie of lage ziekteactiviteit die gekenmerkt werden door het gebruik van een TNFi van de antilichaam subklasse, met een relatief korte ziekte duur van minder dan 10 jaar en een lage MBDA score van kleiner of gelijk aan 44, in staat waren hun TNFi te stoppen zonder dat een exacerbatie volgde gedurende het volgende jaar. Daarentegen moest 80% van vergelijkbare RA patiënten die die een TNFi van de receptor antagonist klasse gebruikte, met een ziekte duur van 10 jaar of langer en een MBDA score van boven de 44 hun TNFi hervatten vanwege klachten of verschijnselen wijzend op exacerbatie van hun RA.

De observatie van de POEET studie dat relatief korte ziekteduur gerelateerd is aan het risico op exacerbaties is in overeenstemming met de studie van Kavanaugh et al., die meldde dat succesvol stoppen van bDMARDS mogelijk was bij RA patiënten met korte ziekteduur. Kuiper et al. daarentegen, waren niet in staat te laten zien dat de ziekteduur van RA patiënten gerelateerd was aan het al dan niet kunnen stoppen van de TNFi behandeling. Mogelijk is het negatieve resultaat van deze laatste studie te verklaren door het beperkte aantal patiënten.

In onze studie waren aanwezigheid van reumafactoren en BMI niet gerelateerd aan het effect van stoppen van TNFi. In tegenstelling tot de Corrona registry en RRR studies die wel een relatie vonden tussen deze predictoren en succesvol stoppen van TNFi. Een mogelijke verklaring voor de afwezigheid van een relatie met reumafactor en anti-CCP zou het hoge percentage dubbel positieve patiënten in onze studie kunnen zijn. Klachten of verschijnselen van resterende ziekteactiviteit ten tijde van het stoppen lijken wel een predictor te zijn van exacerbatie na het stoppen van TNFi. De associatie met een hoge MBDA score bij studiestart in onze POEET studie lijkt in overeenstemming met deze hypothese.

We vonden daarnaast dat het type TNFi ook een predictor lijkt te zijn. Onze analyses laten zien dat patiënten die een TNFi uit de antilichaam klasse (voornamelijk adalimumab) gebruikten significant vaker succesvol hun TNFi konden stoppen in vergelijking met patiënten die een TNFi receptor antagonist (voornamelijk etanercept) gebruikten. TNFi antilichamen lijken een langdurige ziektecontrole te induceren, mogelijk gerelateerd aan de lange halfwaardetijd, door inductie van apoptose van TNF bindende of dragende bloedcellen. Onze bevindingen komen overeen met de recente studie van Hashimoto et al.

De informatie verkregen in hoofdstuk 3, gecombineerd met de theorie uit hoofdstuk 1, lijkt steun te geven aan de “window of opportunity”, de rol van resterende smeulende ziekteactiviteit, en het aangrijpingspunt / mechanisme van de TNFi bij het stoppen van TNFi. Vanzelfsprekend kunnen deze analyses, die achteraf zijn verricht niet de theorie bewijzen maar wel steunen ze de onderliggende hypothesen.

Hoofdstuk4
De multi-biomarker disease activity (MBDA) bloedtest maakt gebruik van 12 biomarkers om een score te berekenen die valide is gebleken als ziekteactiviteitparameter voor RA patiënten. MBDA scores reflecteren de actuele ziekteactiviteit en veranderingen daarvan door de tijd, inclusief effecten van behandelingen met TNFi van RA patiënten. In dit vierde hoofdstuk bestudeerden we deze MBDA score als een voorspeller van exacerbatie na stoppen van TNFi behandeling. We gebruikten de gegevens van de patiënten die gerandomiseerd waren naar de stopgroep. Van nagenoeg al deze patiënten waren serum monsters ten tijde van de start van de studie aanwezig om de MBDA test te doen waardoor de baseline score gebruikt konden worden. We lieten zien dat patiënten met een relatief hoge MBDA score ten tijde van het stoppen van TNFi, significant vaker een exacerbatie kregen tijdens de twaalf maanden observatie. De resultaten suggereren dat een hoge MBDA score, hoewel de patiënten in remissie of lage ziekteactiviteit zijn, een teken kan zijn van resterende ziekteactiviteit. Verschillende voorgaande studies hebben verhoogde MBDA scores in RA patiënten in remissie of lage ziekteactiviteit gevonden. We konden, naar ons weten, als eerste melden dat de MBDA score voorspellende waarde heeft voor het risico op exacerbatie na stoppen van TNFi.
Ten aanzien van de drie verschillende definities van exacerbatie in de POEET studie (TNFi hervatten, medicatie-escalatie en exacerbatie gerapporteerd door de behandelaar), was een hoge MBDA score voor elke definitie steeds een onafhankelijke voorspeller van exacerbatie, maar dit bleef niet zo als we corrigeerden voor alle potentiele voorspellers inclusief de DAS28 scores.
Hoewel de heterogeniteit van RA, en als consequentie daarvan het moeilijk vaststellen van ziekteactiviteit, goed bekend is, lijken laboratoriummethodes (biomarkers) zoals de MBDA score niet in staat de beperkingen van samengestelde klinische uitkomstmaten te verbeteren. De resultaten van de POEET studie bevestigen dat er een relatie bestaat tussen RA ziekteactiviteit en de MBDA score. maar deze relatie is niet erg sterk en rechtvaardigt mogelijk niet de kosten van de test.

Hoofdstuk 5
Naast het biomedische perspectief van de ziekte, is conceptueel het perspectief van de patiënt de spiegel van de ziekteconsequenties voor de patiënt en diens gezondheidsstatus. Daarom hebben we in de POEET studie in aanvulling op de biomedische resultaten ook onderzoek gedaan naar de gevolgen voor de patiënt We hebben aangetoond dat stoppen van TNFi een significant maar kortdurend effect heeft op patiënt-gerapporteerde uitkomstmaten (PROs). zoals de fysieke en geestelijke gezondheidsstatus en gezondheidsgerelateerde utiliteit pijn, beperkingen en moeheid.
Slechts enkele andere studies analyseerden het effect van TNFi stoppen op de door de patiënten ervaren ziektelast. De gerandomiseerde PRESERVE trial liet na 12 maanden zien dat patiënten die etanercept met methotrexaat bleven gebruiken beter scoorden ten aanzien van algemene gezondheid. pijn, beperkingen. gezondheidsutiliteiten. slaap en moeheid in vergelijking met de patiënten die etanercept stopten en alleen methotrexaat gebruikten. Aanvullend liet de observationele RRR studie na 1 jaar zien dat de gemiddelde fysieke beperkingen (HAQ-DI scores) lager (beter) waren in patiënten die in remissie bleven na het stoppen van infliximab in vergelijking tot patiënten die een ziekte--exacecbatie

doormaakten na stoppen. Dit resultaat werd echter niet gevonden in de OPTIMA of de AOMIRE studie. Ook de resultaten van de open-label, niet gerandomiseerde HONOR studie liet geen verschil zien ten aanzien van HAQ-DI scores een jaar na stoppen van adalimumab tussen patiënten die in remissie bleven of patiënten die een exacerbatie kregen. In een erg kleine observationele studie van 21 patiënten. vonden Brocq et al. geen significante verschillen gedurende een jaar ten aanzien van HAQ-DI scores in patiënten die TNFi stopten.
In het algemeen kunnen we concluderen dat de negatieve biomedische effecten van het stoppen van TNFi in RA patiënten ook te zien zijn in de ongunstigere patiënt-gerapporteerde uitkomsten. Maar, in overeenstemming met de zorgvuldige zorg ontwerpen van de verschillende studies, zijn de ongunstigere uitkomsten gering en van korte duur, zonder noemenswaardige invloed op de lange termijn gezondheid van patiënten die proberen hun kostbare behandelingen te stoppen of de dosis ervan te verminderen.

Hoofdstuk 6
Omdat de kosten van geneesmiddelen een van de belangrijke argumenten was in de discussie over stoppen van biologicals, is een kostenanalyse van stoppen versus doorgaan met TNFi behandeling in het geval van goede ziektecontrole (remissie of LDA zoals gedefinieerd door de DAS28) vanzelfsprekend relevant. We hebben laten zien dat stoppen met TNFi in deze groep RA patiënten kosten kan besparen, maar dit betekent wel dat er een klein verlies optreedt aan gezondheidsutiliteiten, zoals gemeten middels quality-adjusted life years (QALYs). De gemiddelde bespaarde kosten waren €368.269 per verloren QALY. We lieten zien dat, met uitzondering van het eerste evaluatiemoment na stoppen, de gemiddelde gezondheidsutiliteit niet significant verschilde gedurende de studieperiode tussen patiënten die stopten of doorgingen met hun TNFi. De resultaten suggereren dat stoppen van TNFI in goed gecontroleerde RA patiënten leidt tot aanzienlijke kostenbesparingen en beperkt en tijdelijk verlies aan gezondheidsgerelateerde kwaliteit van leven.
In de, ook Nederlandse, DRESS studie (dosis verlagen) lieten de onderzoekers zien dat gecontroleerde dosisverlaging van TNFi €390.493 kan besparen voor elke verloren QALY, opvallend vergelijkbaar met stoppen van TNFi in onze POEET stop studie. In een nadere kostenanalyse gebaseerd op de STRASS studie, rapporteerden de auteurs dat een dosisvertagîng strategie €53.417 bespaart per verloren QALY. In de PRESERVE studie, eveneens met dosisreductie in geval van remissie als bestudeerde strategie, melden Kobelt et al. een bedrag tussen €14.000 and €29.000 per gewonnen QALY voor de dosis halvering strategie ten opzichte van de volledige stop van etanercept De auteurs suggereerden dal een dosisreductie ten opzichte van stoppen de meest voordelige strategie is voor patiënten met milde RA, hoewel kostenbesparing van stoppen versus ongewijzigd doorgaan niet separaat gemeld werd.
Sommige studie rapporteerden slechts de kosten van bespaarde geneesmiddelen. Van der Maas et al. rapporteerden een gemiddelde kostenbesparing van €3.474 per patiënt ten gunste van dosisverlaging van infliximab. Een vergelijkbare studie door Murphy et al. in een cohort van 79 patiënten met behalve RA ook artritis psoriatica en ankyloserende spondylitis rapporteerde een gemiddelde besparing van €3.800 per patient per jaar ten gunste van dosisreducties van etanercept of adalimumab.

Hoofdstuk 7
In dit hoofdstuk verrichtten we een zogenaamde post-hoc analyse op de gegevens van de POEET studie om de meest bruikbare meetmethode vast te stellen voor exacerbatie van de ziekte. We toonden aan dat de samengestelde ziekteactiviteitsmaten, globale ziekteactivliteit inschattingen door behandelaar en door patiënt en zelfgerapporteerde pijnmaten allen gebruikt kunnen worden voor het meten van toename van ziekteactiviteit en opvlammingen van ziekte bij RA. Eerdere studies hebben gemeld dat pijn de belangrijkste prioriteit voor behandeling is voor patiënten. In andere studies leek juist fysiek functioneren een van de beste indicatoren voor positieve behandelresultaten. Dus de slechte prestatie van fysiek functioneren in onze studie analyse contrasteert met voorgaande onderzoek naar verbeteringen in plaats van verslechteringen van RA ziekteactiviteit.
In onze analyse presteerden de CDAI, SDA! en DAS28 gelijkwaardig als proxy voor exacerbatie van ziekte activiteit. Vergelijkbare resultaten werden gemeld voor deze samengestelde scores in twee eerdere studies. Acute fase reacties daarentegen lijken weinig aanvullende waarde te hebben over exacerbatie van ziekteactiviteit. De resultaten bieden geen steun aan het recent gesuggereerde toevoegen van moeheid, emotioneel welbevinden of participatie aan een samengestelde maat voor ziekteactiviteit, omdat geen van deze maten veel bijdraagt aan de voorspelling van een exacerbatie van de ziekte. Eerdere studies konden ook geen relevante responsivitett aantonen voor participatie en emotioneel welbevinden.

Conclusie
Vanwege de potentiele risico's maar vooral vanwege toenemende kosten van langdurige TNFi behandeling in groeiende patiëntaantallen, werd het belangrijk gevonden te onderzoeken of RA patiënten met goed gecontroleerde ziekteactiviteit, gedefinieerd als DAS28 remissie of lage ziekteactiviteit, veilig en succesvol hun behandeling met TNA kunnen onderbreken. Het antwoord op de eerste studievraag is dat TNfi stoppen leidt tot een drievoudig verhoogd risico op exacerbatie van de ziekteactiviteit gedurende de studieduur van 12 maanden. Vanzelfsprekend kan het stoppen van anti.reumatische therapie, in dit geval TNFi behandeling, alleen worden overwogen in patiënten bij wie het beoogde behandelresultaat is behaald. Het behoeft geen betoogd dat in gevallen waar het behandelresultaat niet wordt gehaald, intensivering van de behandeling aanbevolen is. We realiseren ons dat een intensieve discussie over de operationalisatie van de definitie van remissie voortduurt Onze studieresultaten ondersteunen de wenselijkheid van een definitie van remissie enerzijds zonder resterende, smeulende ziekteactiviteit als de patiënt voldoet aan de definitie, maar anderzijds zonder classificatie van patiënten zonder ziekteactiviteit als niet in remissie. Hoe dan ook. een wereldwijd bruikbare operationalisatie van de definitie van remissie blijft een uitdaging die verder reikt dan de scope van dit proefschrift. Hoewel de definitie van exacerbatie (flare) ook verschilt tussen studies, lieten wij zien dat een gevoeligheidsanalyse, gebruikmakende van meerdere definities van flare, geen invloed had op de conclusie.
Omdat RA een levenslange ziekte is, blijft hel onderbreken van een succesvolle behandling met anti-reumamedicatie een risico. Succesvol stoppen van TNFi lijkt echter een optie te zijn voor een subgroep van patiënten, maar betekent ook een risico op ziekte exacerbaties. Een risico dat in de POEET, en andere studies, gebleken is hanteerbaar te zijn. Het is belangrijk om van te voren zo goed mogelijk die patiënten te identificeren die het risico lopen op exacerbatie na stoppen versus hen die dat minder hebben. Wij lieten zien dat stoppen met TNR geen langdurige

consequenties lijkt te hebben voor uitkomsten die van belang zijn voor patiënten. Als laatste lieten onze bevindingen zien dat stoppen van TNFi in RA patiënten die goed onder controle zijn kosteneffectief is, maar resulteert in een klein verlies van gezondheidsutiliteit.
Concluderend, stoppen met TNFi in goed gecontroleerde RA patiënten is een realistische optie. Vanzelfsprekend dient het besluit te stoppen met TNFi, of om de dosis te verlagen, een gezamenlijke beslissing te zijn van de patiënt en de behandelend reumatoloog.

Reumatologie

Gout: Patients, medicine and society

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Twente, op
gezag van Rector Magnificus
prof. dr. T.T.M. Palstra,
volgens besluit van het College voor Promoties in
het openbaar te verdedigen
op donderdag 11 juli 20919 om 10:45 uur

door

Carly Ann Janssen
geboren op 27 december 1988
te Nijmegen, Nederland

Promotor: Prof. dr. M.A.F.J. van de Laar
Copromotoren: Dr. H.E. Vonkeman
Dr. M.A.H. Oude Voshaar

Samenvatting

Jicht: patiënten, geneeskunde en de maatschappij

Jicht is een veelvoorkomende inflammatoire gewrichtsaandoening behorend tot de reumatische aandoeningen. Het wordt veroorzaakt door neergeslagen urinezuurkristallen in de synoviaal vloeistof van gewrichten als gevolg van langdurige hyperurikemie. Het (plotseling) optreden van een dergelijke ontstekingsreactie wordt vaak een acute jichtaanval genoemd en is gekenmerkt door symptomen van pijn. zwelling. roodheid en gewrichtsgevoeligheid. Herhaalde aanvallen van acute jicht kunnen leiden tot verergering van de ziekte en ophoping van urinezuurkristallen in gewrichten en weefsel. ook wel (chronische) tofeuze jicht (jichtknobbels) genoemd. Over het algemeen kan jicht leiden tot een verminderde kwaliteit van leven en verminderd fysiek functioneren.

In dit proefschrift worden verschillende onderzoeken gepresenteerd op het gebied van jicht en hyperurikemie. Het proefschrift is opgedeeld in drie delen. Het eerste gedeelte bevat studies die zich richten op de klinische behandelingen van jicht en hyperurikemie. De studies die in het tweede deel van dit proefschrift worden beschreven richten zich op het meten van de gevolgen van jicht vanuit het perspectief van de patiënt met behulp van patiënt gerapporteerde uitkomstmaten (PROMs). In het derde gedeelte wordt ingegaan op de maatschappelijke ziektelast van jicht en hyperurikemie in termen van de kosten en effectiviteit van de verschillende behandelingen voor deze ziektes.

Deel 1: Klinische behandeling van jicht en hyperurikemie

Een acute jichtaanval is goed te behandelen met een van de drie standaard behandelingen: colchicine. niet-steroïde anti-inflammatoire geneesmiddelen of corticosteroïden. Echter, veel patiënten met jicht hebben comorbiditeiten die behandeling met deze middelen bemoeilijkt wegens contra-indicaties. Ook wordt door de aanwezigheid van bijwerkingen of intoleranties in sommige gevallen de behandeling van een acute jichtaanval bemoeilijkt. Voor patiënten die niet behandeld kunnen worden met een van de standaardbehandelingen. bevelen jicht richtlijnen een behandeling met een interleukine-1 (IL-1) remmer aan. Tot op heden is in Europa alleen tegen hoge kosten enkel de IL-remmer canakinumab beschikbaar voor patiënten met 3 aanvallen per jaar en die niet behandeld kunnen worden met standaardzorg. Anakinra is een alternatieve. goedkopere. IL-1 remmer. Uit verschillende observationele studies is al gebleken dat anakinra mogelijk effectief zou kunnen zijn voor het behandelen van acute jicht. Echter. tot op heden zijn er nog geen gerandomiseerde klinische studies geweest om dit te bevestigen.

De studie in **Hoofdstuk 2** van deze thesis had als doel te bepalen of een 5-daagse behandeling van een dagelijkse 100 mg subcutane injectie van de IL-1 receptorantagonist anakinra. een effectief en veilig behandelingsalternatief zou zijn voor de behandeling van acute jichtaanvallen. Om dit te bepalen is er in Nederland een multicenter, dubbelblind, dubbel dummy, gerandomiseerd, actief-gecontroleerd, *non-inferiority (NI)* (niet inferieur aan) studie ontworpen en uitgevoerd, waarbij anakinra werd vergeleken met standaardzorg (colchicine, naproxen of prednison). In totaal zijn 88 mensen geïncludeerd, waarvan 45 en 43 patiënten behandeld zijn met respectievelijk standaardzorg en anakinra. Anakinra was *non-inferior* aan standaardzorg in het verminderen van pijn klachten in patiënten met een acute jichtaanval. Ook daalden in beide behandelingsgroepen in gelijke mate van dag één

tot vijf andere jicht-gerelateerde symptomen zoals gewrichtsgevoeligheid en zwelling. De resultaten van deze studie suggereren dat anakinra een effectieve IL-1 remmer is voor de behandeling van acute jichtaanvallen.

Het verlagen van serum urinezuur (SUZ) spiegels bij patiënten met jicht vormt een belangrijk onderdeel van het behandelingsplan. Dit is onder andere omdat verlaagde SUZ spiegels tot onder de drempelwaarde van urinezuur kristalformatie in verband is gebracht met een verminderd risico op het krijgen van jichtaanval recidieven. Voor het verlagen van de SUZ spiegels in patiënten met jicht wordt daarom behandeling met urinezuurverlagende therapie (UVT) aanbevolen. Echter. zelfs bij jicht patiënten die behandeld worden met lNT zijn jicht recidieven veelvoorkomend, met name in de periode direct na het starten van lNT.

In de studie in **Hoofdstuk 3** werd de prognostische waarde van verschillende klinische. demografische en patiënt-gerapporteerde factoren voor het voorspellen van vroege (<= 3 maanden) jichtaanval recidieven onderzocht bij patiënten die UVT zijn gestart tijdens een acute jichtaanval (N= 75). Binnen de eerste drie maanden had 48% (n= 36) van de patiënten opnieuw een jichtaanval. Resultaten van de binaire multivariate regressie analyse lieten zien dat geen profylaxe bij het starten van UVT (odds ratio (OR) 11.56) en c-reactief proteïne> 30 mg/L (OR 9.47), onafhankelijke voorspellers waren voor een recidief van een jichtaanval binnen de eerste 3 maanden na baseline.

Momenteel is weinig bekend over de mogelijke toegevoegde waarde van het toepassen van een *treat-to-torget (T2T)* strategie (behandelen naar een vooraf bepaald doel/target) in de klinische praktijk voor het verlagen van SUZ spiegels met UVT in patiënten met jicht. Echter. een T2T strategie bij behandeling met UVT wordt momenteel wel aanbevolen door verschillende jicht richtlijnen voor het verlagen van SUZ spiegels.

Hoofdstuk 4 presenteert de resultaten van een klinische audit van *real-world* jichtpatiënten (patiënten zoals gezien in de dagelijkse klinische praktijk) die behandeld werden met beschikbare UVT conform het T2T concept. Voor dat laatste werden de SUZ targets aangehouden (< 360 µmol/L en < 300 µmol/L) van de European League Against Rheumatism. Voor deze retrospectieve studie zijn de medische patiëntendossiers van jicht patiënten uit twee verschillende ziekenhuizen in Nederland onderzocht. De resultaten laten zien dat het SUZ doel van < 360 µmol/L in 83% van de gevallen werd bereikt in de dagelijkse klinische praktijk met de huidige beschikbare UVT en een behandelingswijze conform de T2T strategie. In meer dan de helft van de patiënten (59%) werd ook de SUZ target van < 300 µmol/L bereikt. Deze resultaten suggereren dat het concept T2Twerkt bij de behandeling van jicht en dat de toepassing van deze strategie in de klinische praktijk kan bijdragen bij het verhogen van het percentage jicht patiënten met SUZ spiegels op target.

Verschillende internationale studies tonen aan dat de therapietrouw van langdurig UVT suboptimaal is bij patiënten met jicht. Tot op heden is onbekend of dit ook geldt voor patiënten met jicht en hyperurikemie in Nederland.

In de studie in **Hoofdstuk 5** is de therapietrouw (compliance en persistence) van patiënten met jicht en hyperurikemie bepaald middels het analyseren van uitgegeven

UVT medicatie recepten afkomstig van een landelijk representatieve database. De naleving van voorgeschreven medicatie (*compliance*) was na één jaar 51.7%. wat inhoudt dat iets meer dan de helft van de patiënten UVT-dekking had voor 80% van de dagen in een jaar. Na een jaar zette 42.7% van de patiënten de medicatie nog voort (*persistence*). zonder dat een reli/1-gap (tijdsduur voor het ophalen van herhaalrecepten) van 30 dagen werd overschreden. Toenemende leeftijd. het zijn van een man en wanneer het eerste UVT recept door een reumatoloog werd voorgeschreven waren factoren geassocieerd met een toenemende therapietrouw (zowel *compliance* als *persistence*). De resultaten van dit onderzoek suggereren dat de therapietrouw van UVT in Nederland suboptimaal is en niet conform de jichtrichtlijnen die levenslange behandeling met UVT aanbevelen. Toekomstige studies zijn gewenst naar de redenen van stoppen en naar manieren om therapietrouw te verbeteren.

Deel II: Patiënt-gerapporteerde uitkomstmaten (PROMs) in jicht
PROMs (instrumenten) worden veel gebruikt in studies met jicht om inzicht te krijgen wat de gevolgen van ziekte zijn vanuit de perspectief van de patiënt. Bij het gebruik van PROMs is het belangrijk dat de meeteigenschappen goed onderbouwd zijn zodat de gemeten uitkomsten betrouwbaar zijn.

Hoofdstuk 6 presenteert de resultaten van een systematische literatuur studie die gericht was op het identificeren van alle beschikbare PROMs voor jicht en kritisch te beoordelen wat de inhoudsvaliditeit en andere meeteigenschappen (betrouwbaarheid. gevoeligheid voor verandering, construct validiteit, vloer- en plafondeffecten) van deze PROMs zijn. De zoekopdracht resulteerde in 13 PROMs. die bijna alle uitkomstdomeinen omvatten die zijn goedgekeurd voor gebruik bij acute en chronische jicht studies. Opmerkelijk was dat voor het meten van patiënt-gerapporteerde gewrichtszwelling en gewrichtsgevoeligheid geen PROMs en voor specifiek jicht slechts drie PROMs beschikbaar waren. Resultaten van deze studie lieten zien dat de subschaal voor fysiek functioneren van de Short Form-36 item versie 2. de enige PROM is waarvoor voldoende bewijs was voor de psychometrische eigenschappen die in deze studie werden onderzocht. Vanuit het bredere perspectief bleek uit dit onderzoek dat voor veel van de PROMs die in klinische studies bij jicht gebruikt worden. de meeteigenschappen nog niet goed ondersteund zijn.

Het doel van de studie in **Hoofdstuk 7** was om een gemiddelde score te ontwikkelen die de algehele intensiteit van een jichtaanval weergeeft. de Gout Attack lntensity Score (GAIS). samengesteld uit individuele symptoomscores van patiënt-gerapporteerde gewrichtspijn. zwelling en gevoeligheid. gemeten op een 5-punts antwoordschaal. Uit de resultaten bleek dat de GAIS kan worden geïnterpreteerd als een ordinale schaal. waarbij hogere scores een hogere jichtaanval symptoom intensiteit aangeven. De GAIS bleek betrouwbaar en gevoelig te zijn voor verandering. Ook was de GAIS beter in staat onderscheid te maken tussen mensen die wel en niet reageerde op behandeling, in vergelijking tot de individuele items waaruit het bestaat (pijn. zwelling, gevoeligheid). Resultaten van de studie suggereren dat de GAIS gebruikt kan worden in klinische studies naar jicht voor het bepalen van de intensiteit van een jichtaanval.

Deel III: Maatschappelijke ziektelast van jicht (disease burden of gaut)
Het doel van de studie beschreven in **Hoofdstuk 8** was het bepalen van de kosteneffectiviteit van verschillende combinaties van UVT (allopurinol. febuxostat. geen UVTI en anti-inflammatoire behandelingen voor acute jichtaanvallen (colchicine. naproxen. prednison. anakinra). Hiervoor is een gezondheidseconomische evaluatie uitgevoerd op basis van een simulatie op patiëntniveau. Nieuw gediagnosticeerde jicht patiënten. gestart met UVTtijdens een jichtaanval, zijn in het model voor een jaar gevolgd voor het schatten van de kosten en de effectiviteit (uitgedrukt in quality-adjusted life years) van de verschillende behandelingscombinaties voor jicht en hyperurikemie. Het model is de eerste op het gebied van jicht die gelijktijdig de behandelingen van UVT en acute jicht evalueert. In vergelijking met 'Geen UVT' waren zowel allopurinol en febuxostat kosteneffectief. en bij een hogere betalingsbereidheid (willingness-ta-poy) (ongeveer > €25.173) was febuxostat kosteneffectief in vergelijking met allopurinol. in combinatie met verschillende ontstekingsremmende middelen. Voor de behandeling van acute jichtaanvallen en onafhankelijk van welke UVT er werd gebruikt, hadden colchicine. naproxen en prednison vergelijkbare resultaten. hoewel naproxen over het algemeen het meest gunstige profiel op kosteneffectiviteit bood. Met name als gevolg van de hoge kosten per behandeling was anakinra niet kosteneffectief in vergelijking met standaardzorg, al leverde het wel de hoogste utiliteit.

Algehele conclusies
Vanuit een medisch perspectief suggereren onze bevindingen dat de IL-1 remmer anakinra een effectieve behandeling is voor het behandelen van acute jichtaanvallen. Anakinra was non-inferior aan standaardzorg in het verminderen van pijn in patiënten met een acute jichtaanval en het verminderde andere jicht-gerelateerde symptomen in gelijke mate als standaardzorg. Dit ondersteunt verder de validiteit van de rol van IL-1 in jicht. Wij geloven dat anakinra van toegevoegde waarde is voor het behandelen van acute jichtaanvallen als een effectieve. tweedelijnsbehandelingsoptie. Met name voor patiënten met jicht die niet met standaardzorg behandeld kunnen worden door intoleranties. comorbiditeiten of niet succesvol reageren op deze behandelingen. Daarnaast zou anakinra mogelijk kunnen dienen als een doelmatig en goedkoper alternatief voor de IL-1 remmer canakinumab.

Verder bleek de langdurige behandeling van jicht en hyperurikemie suboptimaal te zijn. in termen van UVT therapietrouw in Nederland. maar ook kijkend naar de frequentie van terugkerende jichtaanvallen in patiënten die UVT zijn gestart. Voor het verbeteren van de uitkomsten in patiënten met jicht kan het nodig zijn om UVT therapietrouw vroegtijdig te stimuleren bij het behandelen van jicht en hyperurikemie. mogelijk met behulp van interventies gericht op therapietrouw zoals programma's gecoördineerd door verpleegkundigen. Daarnaast bleek een T2T strategie voor het verlagen van SUZ spiegels met UVT in patiënten met jicht veelbelovend in het behalen van de aanbevolen SUZ targets. Het is echter belangrijk dat de effectiviteit van een T2T strategie voor jicht ondersteund wordt met hoogwaardig bewijs. d.w.z. gerandomiseerde studies. om opheldering en consensus te bereiken over de beste. langdurige strategie om patiënten met jicht en hyperurikemie te behandelen voor het verlagen van SUZ spiegels met UVT.

Tot slot toont deze thesis aan dat er meer bewijs over de meeteigenschappen van veelgebruikte PROMs in jicht beschikbaar moet komen. idealiter gebaseerd op moderne psychometrische technieken en methodologisch degelijke studies. Daarnaast kan de GAIS worden gebruikt in studies van acute jicht voor het bepalen van de intensiteit van een jichtaanval. De brede adopti e van de GAIS zou de standaardisatie van uitkomstmaten in acute jicht studies kunnen stimuleren. wat de vergelijking van patiënt-gerapporteerde uitkomsten tussen deze studies zou kunnen verbeteren.

PubMed publicaties per vakgroep
Anesthesie

1. Dutch combat operation experiences in Iraq and Afghanistan: The conundrum of low surgical workload deployments
Vermeulen CFW, Keijzers PJ, Fredriks EHWM, van der Hee P, Van Waes OJF, Hoencamp R

Introduction: The Combined Joined Task Force - Operation Inherent Resolve is the military intervention of Iraq and Coalition Forces in the battle against Islamic State of Iraq and Syria (ISIS). Al Assad Airbase (AAAB) is one of the key airbases. It contains a Role 2 Medical Treatment Facility, primarily to perform Damage Control Surgery in Coalition Forces, Iraqi National Security Forces and Local Nationals. We present a six month medical exposure in order to provide insight into the treatment of casualties and to optimize medical planning of combat operations and (pre-/post-) deployment training.
Patients and methods: This is a cohort study of casualties that were admitted to the Role 2 Medical Treatment Facility AAAB from November 2017 to April 2018. Their mechanisms and types of injury are described and compared to those sustained in Uruzgan, Afghanistan between 2006-2010. Additionally, they are compared to the caseload in the Dutch civilian medical centers of the medical specialist team at AAAB.
Results: There were significant differences in both mechanism and type of injury between Coalition Forces and Iraqi Security Forces ($p = 0.0001$). Coalition Forces had 100% disease and non-battle injuries, where Iraqi Security Forces had 86% battle injuries and 14% non-battle casualties. The most common surgical procedures performed were debridement of wounds (38%), (exploratory) laparotomy (10%) and genital procedures (7%). The surgical caseload in Uruzgan, Afghanistan was significantly different in aspect and quantity, being 4.1 times higher. When compared to the workload at home all team members had at least a tenfold lower workload than in their civilian hospitals.
Discussion: The deployed surgical teams were scarcely exposed to casualties at AAAB, Iraq. These low workload deployments could cause a decline in surgical skills. Military medical planning should be tailormade and should include adjusting length of stay, (pre-/post-)deployment refresher training and early consultation of military medical specialists. Future research should focus on optimizing this process by investigating fellowships in combat matching trauma centers, regional and international collaboration and refresher training possibilities to maintain the expertise of the acute military care provider.

Gepubliceerd: Injury 2019;50(1):215-9
Impact factor: 1.834; Q2

Totale impact factor: 1.834
Gemiddelde impact factor: 1.834

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 1.834
Gemiddelde impact factor: 1.834

Cardiologie

1. Impact of Diabetes Mellitus in Women Undergoing Percutaneous Coronary Intervention With Drug-Eluting Stents
Baber U, Stefanini GG, Giustino G, Stone GW, Leon MB, Sartori S, Aquino M, Steg PG, Windecker S, Wijns W, Serruys PW, Valgimigli M, Morice MC, Camenzind E, Weisz G, Smits PC, Kandzari DE, von Birgelen C, Dangas GD, Galatius S, Jeger RV, Kimura T, Mikhail GW, Itchhaporia D, Mehta L, Ortega R, Kim HS, Kastrati A, Chieffo A, Mehran R

Background: Data examining the impact of diabetes mellitus (DM) on ischemic risk after percutaneous coronary intervention in women are limited as most clinical trial participants are male. We evaluated (1) the impact of DM on ischemic outcomes in women undergoing drug-eluting stent (DES) implantation and (2) whether the outcomes of new- versus early-generation DES vary by DM status.
Methods and Results: We pooled patient-level data of 10 448 women undergoing percutaneous coronary intervention with DES from 26 randomized trials. Baseline characteristics and 3-year clinical outcomes were stratified according to DM status (noninsulin-dependent and insulin-dependent) and DES generation. The primary end point was the composite of all-cause death or myocardial infarction. Secondary end points were definite or probable stent thrombosis and target lesion revascularization. Compared with women without DM (n=7154, 68.5%), adjusted risks (adjusted hazard ratios [95% CI]) for death or myocardial infarction among women with noninsulin-dependent DM (n=2241, 21.4%) and insulin-dependent DM (n=1053, 10.1%) were 1.30 (1.11-1.53) and 1.71 (1.41-2.07), respectively (Ptrend<0.001). Similar trends were observed for def/prob stent thrombosis and target lesion revascularization. Compared with early-generation DES, use of newer-generation DES was associated with significant reductions in death or myocardial infarction in the absence of DM whereas differences were nonsignificant in the presence of DM, with similar findings for def/prob stent thrombosis and target lesion revascularization.
Conclusions: The presence of DM is associated with substantial, graded, and durable risks for ischemic events among women undergoing percutaneous coronary intervention with DES. The safety and efficacy profile of newer-generation DES is preserved among women without DM, while benefits are nonsignificant among women with DM.

Gepubliceerd: Circ Cardiovasc Interv 2019 Jul;12(7):e007734
Impact factor: 6.088; Q1

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2. Incidence and predictors of implantable cardioverter-defibrillator therapy and its complications in idiopathic ventricular fibrillation patients
Blom LJ, Visser M, Christiaans I, Scholten MF, Bootsma M, van den Berg MP, Yap SC, van der Heijden JF, Doevendans PA, Loh P, Postema PG, Barge-Schaapsveld DQ, Hofman N, Volders PGA, Wilde AA, Hassink RJ

Aims: Idiopathic ventricular fibrillation (IVF) is a rare cause of sudden cardiac arrest. Implantable cardioverter-defibrillator (ICD) implantation is currently the only treatment option. Limited data are available on the prevalence and complications of ICD therapy

in these patients. We sought to investigate ICD therapy and its complications in patients with IVF.
Methods and Results: Patients were selected from a national registry of IVF patients. Patients in whom no underlying diagnosis was found during follow-up were eligible for inclusion. Recurrence of ventricular arrhythmia (VA) was derived from medical and ICD records, electrogram records of ICD therapies were used to differentiate between appropriate or inappropriate interventions. Independent predictors for appropriate ICD shock were calculated using cox regression. In 217 IVF patients, recurrence of sustained VAs occurred in 66 patients (30%) during a median follow-up period of 6.1 years. Ten patients died (4.6%). Thirty-eight patients (17.5%) experienced inappropriate ICD therapy, and 32 patients (14.7%) had device-related complications. Symptoms before cardiac arrest [hazard ratio (HR): 2.51, 95% confidence interval (CI): 1.48-4.24], signs of conduction disease (HR: 2.27, 95% CI: 1.15-4.47), and carrier of the DPP6 risk haplotype (HR: 3.24, 1.70-6.17) were identified as independent predictors of appropriate shock occurrence.
Conclusion: Implantable cardioverter-defibrillator therapy is an effective treatment in IVF, treating recurrences of potentially lethal VAs in approximately one-third of patients during long-term follow-up. However, device-related complications and inappropriate shocks were also frequent. We found significant predictors for appropriate ICD therapy. This may imply that these patients require additional management to prevent recurrent events.

Gepubliceerd: Europace 2019 Oct 1;21(10):1519-26
Impact factor: 5.047; Q1

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3. Intracavitary course of right coronary artery
Bouhuijzen LJ, Kardux JJ, Braam RL

Gepubliceerd: Neth Heart J 2019 Jun;27(6):335-6
Impact factor: 1.972; Q3

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4. Derivation and external validation of a novel risk score for prediction of 30-day mortality after percutaneous coronary intervention
Brener SJ, Leon MB, Serruys PW, Smits PC, von Birgelen C, Mehran R, Kirtane AJ, Witzenbichler B, Rinaldi MJ, Metzger DC, Mazzaferri EL, Jr., Zhang Z, Stone GW

Aims: Early mortality after percutaneous coronary intervention (PCI) is relatively rare. Current risk prediction models for this event are outdated. We sought to derive a 30-day mortality risk score after PCI.
Methods and Results: The score was derived from a pooled database of 21 randomised clinical trials using a logistic regression model incorporating clinical and angiographic variables. The score was validated in a separate unrestricted study population, the Assessment of Dual AntiPlatelet Therapy With Drug Eluting Stents (ADAPT-DES) registry. Of 32,882 eligible patients, 75% had data for all 19 variables used for score derivation. The independent predictors of 30-day mortality were age, presentation with ACS, diabetes mellitus, use of first-generation drug-eluting stents, left main or left anterior descending artery lesion, prior myocardial infarction (MI), and suboptimal flow in the artery before or after PCI. The median [interquartile range]

score in the derivation cohort was 5 [3, 6] and overall mortality was 0.49%, ranging from 0.08% to 1.64% with scores of 0-16. The 30-day mortality rate was approximately tenfold higher in patients with a score at or above versus below the median of 5 (0.86% versus 0.08%, p<0.0001). Discrimination in both cohorts was very good (C statistic=0.848 and 0.828, respectively), and calibration was satisfactory.
Conclusions: A novel risk score incorporating eight readily available clinical and angiographic variables had high discrimination for 30-day death after PCI across a wide range of clinical scenarios.

Gepubliceerd: EuroIntervention 2019 Aug 9;15(6):e551-e557
Impact factor: 4.018; Q2

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5. Outcomes in Patients Treated With Thin-Strut, Very Thin-Strut, or Ultrathin-Strut Drug-Eluting Stents in Small Coronary Vessels: A Prespecified Analysis of the Randomized BIO-RESORT Trial
Buiten RA, Ploumen EH, Zocca P, Doggen CJM, van der Heijden LC, Kok MM, Danse PW, Schotborgh CE, Scholte M, de Man FHAF, Linssen GCM, von Birgelen C

Importance: Stenting small-vessel lesions has an increased adverse cardiovascular event risk. Very thin-strut or ultrathin-strut drug-eluting stents might reduce this risk, but data are scarce.
Objective: To assess the outcome of all-comer patients with small coronary vessel lesions treated with 3 dissimilar types of drug-eluting stents.
Design: This is a prespecified substudy of the Comparison of Biodegradable Polymer and Durable Polymer Drug-eluting Stents in an All Comers Population (BIO-RESORT) trial, an investigator-initiated, randomized, patient-blinded comparative clinical drug-eluting stent trial. Patients treated with ultrathin-strut sirolimus-eluting stents, very thin-strut everolimus-eluting stents, or previous-generation thin-strut zotarolimus-eluting stents were enrolled from December 2012 to August 2015. This multicenter trial was conducted in 4 Dutch centers for cardiac intervention. Of all 3514 all-comer BIO-RESORT participants, 1506 patients with treatment in at least 1 small-vessel lesion (reference vessel <2.5 mm) were included. Data were analyzed between September 2018 and February 2019.
Main Outcomes and Measures: Target lesion failure at 3-year follow-up, a composite of cardiac death, target vessel-related myocardial infarction, or target lesion revascularization, analyzed by Kaplan-Meier methods.
Results: In 1452 of 1506 participants (96.4%) (1057 men [70.2%]; 449 women [29.8%]; mean [SD] age, 64.3 [10.4] years), follow-up was available. Target lesion failure occurred in 36 of 525 patients (7.0%) treated with sirolimus-eluting stents, 46 of 496 (9.5%) with everolimus-eluting stents, and 48 of 485 (10.0%) with zotarolimus-eluting stents (sirolimus-eluting vs zotarolimus-eluting hazard ratio [HR], 0.68; 95% CI, 0.44-1.05; P = .08; everolimus-eluting vs zotarolimus-eluting HR, 0.93; 95% CI, 0.62-1.39; P = .72). There was a difference in target lesion revascularizations between sirolimus-eluting and zotarolimus-eluting stents (2.1% vs 5.3%; HR, 0.40; 95% CI, 0.20-0.81; P = .009) that emerged after the first year of follow-up (1.0% vs 3.7%; P = .006); multivariate analysis showed that sirolimus-eluting stent implantation was independently associated with a lower target lesion revascularization rate at 3-year follow-up (adjusted HR, 0.42; 95% CI, 0.20-0.85; P = .02). In the everolimus-

eluting stents, the revascularization rate was 4.0% (vs zotarolimus-eluting, HR, 0.74; 95% CI, 0.41-1.34; P = .31). There was no significant between-stent difference in cardiac death, target vessel myocardial infarction, or stent thrombosis.
Conclusions and Relevance: Patients stented in small coronary vessels experienced fewer repeated revascularizations if treated with ultrathin-strut sirolimus-eluting stents vs previous generation thin strut zotarolimus-eluting stents. Further research is required to evaluate the potential effect of particularly thin stent struts.
Trial Registration: ClinicalTrials.gov identifier: NCT01674803.

Gepubliceerd: JAMA Cardiol 2019 Jul 1;4(7):659-69
Impact factor: 11.866; Q1

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6. Thin, Very Thin, or Ultrathin Strut Biodegradable or Durable Polymer-Coated Drug-Eluting Stents: 3-Year Outcomes of BIO-RESORT
Buiten RA, Ploumen EH, Zocca P, Doggen CJM, Danse PW, Schotborgh CE, Scholte M, van Houwelingen KG, Stoel MG, Hartmann M, Tjon Joe Gin RM, Somi S, Linssen GCM, Kok MM, von Birgelen C

Objectives: The aim of this study was to assess the 3-year safety and efficacy of treating all-comer patients with 3 contemporary drug-eluting stents (DES).
Background: The BIO-RESORT (Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population) (TWENTE III) randomized trial (NCT01674803) found similar 1-year safety and efficacy for the 2 biodegradable-polymer DES (i.e., ultrathin-strut cobalt-chromium Orsiro sirolimus-eluting stent [SES] and very-thin-strut platinum-chromium Synergy everolimus-eluting stent) compared with the durable-polymer thin-strut cobalt-chromium Resolute Integrity zotarolimus-eluting stent (ZES). Two-year follow-up suggested that the SES might reduce repeat revascularizations beyond 1 year compared with the ZES.
Methods: A total of 3,514 all-comer patients were treated at 4 centers for coronary intervention. The main clinical endpoint, target vessel failure, was a composite of safety (cardiac death or target vessel-related myocardial infarction) and efficacy (target vessel revascularization). Secondary endpoints included the individual components of target vessel failure and stent thrombosis.
Results: Three-year follow-up data were available for 3,393 of 3,514 patients (96.6%). Target vessel failure occurred in 8.5% with SES and 10.0% with ZES (plog rank = 0.22) and in 8.8% with everolimus-eluting stents (vs. ZES, plog rank = 0.32). Rates of cardiac death, target vessel myocardial infarction, and target vessel revascularization were similar between stent groups. Landmark analyses found no statistically significant between-stent difference in repeat revascularization between 1 and 3 years. Definite or probable stent thrombosis rates were low (SES, 1.1%; everolimus-eluting stent, 1.1%; ZES, 0.9%) and similar with all 3 DES.
Conclusions: Despite substantial differences in stent backbone and polymer coating, all 3 DES showed favorable 3-year safety and efficacy in all comers, without significant between-stent differences. Further follow-up is required to definitely answer the question of whether one stent might improve clinical outcomes at a later stage.

Gepubliceerd: JACC Cardiovasc Interv 2019 Sep 9;12(17):1650-60
Impact factor: 9.544; Q1

7. Impact of Periprocedural Myocardial Biomarker Elevation on Mortality Following Elective Percutaneous Coronary Intervention
Garcia-Garcia HM, McFadden EP, von Birgelen C, Rademaker-Havinga T, Spitzer E, Kleiman NS, Cohen DJ, Kennedy KF, Camenzind E, Mauri L, Steg PG, Wijns W, Silber S, van Es GA, Serruys PW, Windecker S, Cutlip D, Vranckx P

Objectives: This study sought to explore the association between biomarker elevation, with creatine kinase-myocardial band (CK-MB) or cardiac troponin (cTn), following percutaneous coronary intervention (PCI) and mortality in patients undergoing PCI for stable angina with normal baseline values.
Background: Several studies have shown a strong association between post-PCI CK-MB elevation and subsequent mortality. However, the prognostic significance of troponin elevation following coronary intervention is still debated.
Methods: Patient-level data from 5 contemporary coronary stent trials and 1 large registry were pooled. Mortality of patients with stable angina, with normal baseline biomarkers, was compared between patients with and those without different cutoff values of cTn and CK-MB.
Results: A total of 13,452 patients were included in this pooled analysis. The overall percentage of patients with elevated biomarkers following PCI was 23.9% for CK-MB and 68.4% for cTn. In the patient cohort for whom both assays were available (n = 8,859), 2.4% had both CK-MB >/=5 x the upper limit of normal (ULN) and cTn >/=35 x ULN, while 92% had both CK-MB <5 x ULN and cTn <35 x ULN. Among patients with CK-MB >/=5 x ULN (n = 315), 212 (67.3%) also had cTn >/=35 x ULN. Conversely, 390 of patients (64.8%) who had cTn >/=35 x ULN did not have CK-MB >/=5 x ULN. A total of 259 patients (1.9%) died at 1 year; 20 (7.7%) had CK-MB >/=5 x ULN, and 23 (8.8%) had cTn >/=35 x ULN. In the Cox multivariate analysis, in which the CK-MB and cTn ratios post-procedure were forced into the model, age, prior myocardial infarction, lesion complexity, hyperlipidemia, and CK-MB ratio (>/=10) post-procedure were associated with increased 1-year mortality.
Conclusions: Following elective PCI in patients in stable condition treated with second-generation drug-eluting stent, CK-MB and cTn elevations remain common. After multivariate adjustment, there was an increased mortality rate with elevation of CK-MB after PCI, whereas cTn elevation was not independently associated with mortality at 1 year.

Gepubliceerd: JACC Cardiovasc Interv 2019 Oct 14;12(19):1954-62
Impact factor: 9.544; Q1

8. Left ventricular global longitudinal strain and long-term prognosis in patients with chronic obstructive pulmonary disease after acute myocardial infarction
Goedemans L, Abou R, Hoogslag GE, Ajmone MN, Delgado V, Bax JJ

Aims: Left ventricular (LV) systolic function is a known prognostic factor after ST-segment elevation myocardial infarction (STEMI). We evaluated the prognostic value of LV global longitudinal strain (GLS) in patients with chronic obstructive pulmonary disease (COPD) after STEMI.

Methods and results: One hundred and forty-three STEMI patients with COPD (mean age 70 +/- 11 years, 71% male), were retrospectively analysed. Left ventricular ejection fraction (LVEF) and LV GLS were measured on transthoracic echocardiography within 48 h of admission. Patients were followed for the occurrence of all-cause mortality and the combined endpoint of all-cause mortality and heart failure hospitalization. After a median follow-up of 68 (interquartile range 38.5-99) months, 66 (46%) patients died and 70 (49%) patients reached the combined endpoint. The median LV GLS was -14.4%. Patients with LV GLS >-14.4% (more impaired) showed higher cumulative event rates of all-cause mortality (19%, 26%, and 44% vs. 7%, 8%, and 18% at 1, 2, and 5 years follow-up; log-rank P = 0.004) and the combined endpoint (26%, 34%, and 50% vs. 8%, 10%, and 20% at 1, 2, and 5 years follow-up; log-rank P = 0.001) as compared to patients with LV GLS </=-14.4%. In multivariate analysis, LV GLS >-14.4% was independently associated with increased all-cause mortality and the combined endpoint [hazard ratio (HR) 2.07; P = 0.02 and HR 2.20; P = 0.01, respectively] and had incremental prognostic value over LVEF demonstrated by a significant increase in chi2 (P = 0.023 and P = 0.011, respectively).
Conclusion: Impaired LV GLS is independently associated with worse long-term survival in STEMI patients with COPD and has incremental prognostic value over LVEF.

Gepubliceerd: Eur Heart J Cardiovasc Imaging 2019;201(56):65
Impact factor: 5.260; Q1

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9. Diagnosis of obstructive coronary artery disease using computed tomography angiography in patients with stable chest pain depending on clinical probability and in clinically important subgroups: meta-analysis of individual patient data

Haase R, Schlattmann P, Gueret P, Andreini D, Pontone G, Alkadhi H, Hausleiter J, Garcia MJ, Leschka S, Meijboom WB, Zimmermann E, Gerber B, Schoepf UJ, Shabestari AA, Norgaard BL, Meijs MFL, Sato A, Ovrehus KA, Diederichsen ACP, Jenkins SMM, Knuuti J, Hamdan A, Halvorsen BA, Mendoza-Rodriguez V, Rochitte CE, Rixe J, Wan YL, Langer C, Bettencourt N, Martuscelli E, Ghostine S, Buechel RR, Nikolaou K, Mickley H, Yang L, Zhang Z, Chen MY, Halon DA, Rief M, Sun K, Hirt-Moch B, Niinuma H, Marcus RP, Muraglia S, Jakamy R, Chow BJ, Kaufmann PA, Tardif JC, Nomura C, Kofoed KF, Laissy JP, Arbab-Zadeh A, Kitagawa K, Laham R, Jinzaki M, Hoe J, Rybicki FJ, Scholte A, Paul N, Tan SY, Yoshioka K, Rohle R, Schuetz GM, Schueler S, Coenen MH, Wieske V, Achenbach S, Budoff MJ, Laule M, Newby DE, Dewey M

Objective: To determine whether coronary computed tomography angiography (CTA) should be performed in patients with any clinical probability of coronary artery disease (CAD), and whether the diagnostic performance differs between subgroups of patients.
Design: Prospectively designed meta-analysis of individual patient data from prospective diagnostic accuracy studies.
Data sources: Medline, Embase, and Web of Science for published studies. Unpublished studies were identified via direct contact with participating investigators.

Eligibility criteria for selecting studies: Prospective diagnostic accuracy studies that compared coronary CTA with coronary angiography as the reference standard, using at least a 50% diameter reduction as a cutoff value for obstructive CAD. All patients needed to have a clinical indication for coronary angiography due to suspected CAD, and both tests had to be performed in all patients. Results had to be provided using 2x2 or 3x2 cross tabulations for the comparison of CTA with coronary angiography. Primary outcomes were the positive and negative predictive values of CTA as a function of clinical pretest probability of obstructive CAD, analysed by a generalised linear mixed model; calculations were performed including and excluding non-diagnostic CTA results. The no-treat/treat threshold model was used to determine the range of appropriate pretest probabilities for CTA. The threshold model was based on obtained post-test probabilities of less than 15% in case of negative CTA and above 50% in case of positive CTA. Sex, angina pectoris type, age, and number of computed tomography detector rows were used as clinical variables to analyse the diagnostic performance in relevant subgroups.
Results: Individual patient data from 5332 patients from 65 prospective diagnostic accuracy studies were retrieved. For a pretest probability range of 7-67%, the treat threshold of more than 50% and the no-treat threshold of less than 15% post-test probability were obtained using CTA. At a pretest probability of 7%, the positive predictive value of CTA was 50.9% (95% confidence interval 43.3% to 57.7%) and the negative predictive value of CTA was 97.8% (96.4% to 98.7%); corresponding values at a pretest probability of 67% were 82.7% (78.3% to 86.2%) and 85.0% (80.2% to 88.9%), respectively. The overall sensitivity of CTA was 95.2% (92.6% to 96.9%) and the specificity was 79.2% (74.9% to 82.9%). CTA using more than 64 detector rows was associated with a higher empirical sensitivity than CTA using up to 64 rows (93.4% v 86.5%, P=0.002) and specificity (84.4% v 72.6%, P<0.001). The area under the receiver-operating-characteristic curve for CTA was 0.897 (0.889 to 0.906), and the diagnostic performance of CTA was slightly lower in women than in with men (area under the curve 0.874 (0.858 to 0.890) v 0.907 (0.897 to 0.916), P<0.001). The diagnostic performance of CTA was slightly lower in patients older than 75 (0.864 (0.834 to 0.894), P=0.018 v all other age groups) and was not significantly influenced by angina pectoris type (typical angina 0.895 (0.873 to 0.917), atypical angina 0.898 (0.884 to 0.913), non-anginal chest pain 0.884 (0.870 to 0.899), other chest discomfort 0.915 (0.897 to 0.934)).
Conclusions: In a no-treat/treat threshold model, the diagnosis of obstructive CAD using coronary CTA in patients with stable chest pain was most accurate when the clinical pretest probability was between 7% and 67%. Performance of CTA was not influenced by the angina pectoris type and was slightly higher in men and lower in older patients.
Systematic Review Registration: Prospero CRD42012002780.

Gepubliceerd: BMJ 2019 Jun 12;365:l1945
Impact factor: 27.604; Q1

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10. First Report of Edge Vascular Response at 12Months of Magmaris, A Second-Generation Drug-Eluting Resorbable Magnesium Scaffold, Assessed by Grayscale Intravascular Ultrasound, Virtual Histology, and Optical Coherence Tomography. A Biosolve-II Trial Sub-Study

Hideo-Kajita A, Garcia-Garcia HM, Haude M, Joner M, Koolen J, Ince H, Abizaid A, Toelg R, Lemos PA, von Birgelen C, Christiansen EH, Wijns W, Neumann FJ, Kaiser C, Eeckhout E, Teik LS, Escaned J, Azizi V, Kuku KO, Ozaki Y, Dan K, Waksman R

Introduction and Objective: The edge vascular response (EVR) remains unknown in second generation drug-eluting Resorbable Magnesium Scaffold (RMS), such as Magmaris. The aim of the study was to evaluate tissue modifications in the RMS edges over time, assessed by different invasive imaging modalities.
Methods: The patients treated with the device were assessed by optical coherence tomography (OCT), grayscale intravascular ultrasound (IVUS), and virtual histology IVUS at baseline and 12months. The EVR study performed a segment- and frame-level analysis of the 5mm segments proximal and distal of the actual RMS.
Results: The segment-level grayscale IVUS (n=10), virtual histology IVUS (n=10), and OCT (n=18) analysis did not show any significant changes after 12months, except for a fibrous plaque area (FPA) reduction of 0.5mm(2) (p=0.017) in the proximal segment compared to baseline. In the frame-level analysis, IVUS evaluation revealed a vessel area decreased 2.80+/-1.43mm(2) (p=0.012) and 2.49+/-1.53mm(2) (p=0.022) in 2 proximal frames. This was accompanied by plaque area reduction of 0.88+/-0.70mm(2) (p=0.048) and a FPA decreased by 0.63+/-0.48mm(2) (p=0.004) in one proximal frame. In 1 distal frame, there was a dense calcium area reduction of 0.10+/-0.12mm(2) (p=0.045), FPA and fibrous fatty plaque increased 0.54+/-0.53mm(2) (p=0.023) and 0.17+/-0.16mm(2) (p=0.016), respectively. By OCT, there was a lumen area decrease of 0.76+/-1.51mm(2) (p=0.045) in a distal frame.
Conclusion: At 12months, Magmaris EVR assessment does not show overall significant changes, except for a fibrous plaque area reduction in the proximal segment. This could be translated as a benign healing process at the edges of the RMS.

Gepubliceerd: Cardiovasc Revasc Med 2019 May;20(5):392-8
Impact factor: 0; nvt

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11. A Multicenter Comparison of 2 Point-of-Care Activated Clotting Time Test Systems
Kemna EWM, Schellings MWM, Vlachojannis GJ, Falter F, Milane-Santman A, Hesselink T, Scholten M, Krabbe JG

Gepubliceerd: J Appl Lab Med 2019 Nov;4(3):468-70
Impact factor: 0; nvt

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12. Reply to the letter to the editor regarding the article "Prediabetes and its impact on clinical outcome after coronary intervention in a broad patient population"
Kok MM, Sattar N, von Birgelen C

Gepubliceerd: EuroIntervention 2019 Feb 8;14(15):e1621-e1622
Impact factor: 4.018; Q2

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13. Roadmap for cardiovascular education across the European Society of Cardiology: inspiring better knowledge and skills, now and for the future
Kotecha D, Bax JJ, Carrera C, Casadei B, Merkely B, Anker SD, Vardas PE, Kearney PP, Roffi M, Ros M, Vahanian A, Weidinger F, Beeri R, Budaj A, Calabro P, Czerwinska-Jelonkiewicz K, D'Ascenzi F, De Potter T, Fox KF, Hartikainen J, McAdam B, Milicic D, Pasquet AA, Sionis A, Sohaib SMA, Tsioufis C, Verhorst PMJ, Kirchhof P

Aims: The provision of high-quality education allows the European Society of Cardiology (ESC) to achieve its mission of better cardiovascular practice and provides an essential component of translating new evidence to improve outcomes. **Methods and results:** The 4th ESC Education Conference, held in Sophia Antipolis (December 2016), brought together ESC education leaders, National Directors of Training of 43 ESC countries, and representatives of the ESC Young Community. Integrating national descriptions of education and cardiology training, we discussed innovative pathways to further improve knowledge and skills across different training programmes and health care systems. We developed an ESC roadmap supporting better cardiology training and continued medical education (CME), noting: (i) The ESC provides an excellent framework for unbiased and up-to-date cardiovascular education in close cooperation with its National Societies. (ii) The ESC should support the harmonization of cardiology training, curriculum development, and professional dialogue and mentorship. (iii) ESC congresses are an essential forum to learn and discuss the latest developments in cardiovascular medicine. (iv) The ESC should create a unified, interactive educational platform for cardiology training and continued cardiovascular education combining Webinars, eLearning Courses, Clinical Cases, and other educational programmes, along with ESC Congress content, Practice Guidelines and the next ESC Textbook of Cardiovascular Medicine. (v) ESC-delivered online education should be integrated into National and regional cardiology training and CME programmes.
Conclusion: These recommendations support the ESC to deliver excellent and comprehensive cardiovascular education for the next generation of specialists. Teamwork between international, national and local partners is essential to achieve this objective.

Gepubliceerd: Eur Heart J 2019;40(21):1728-38
Impact factor: 24.889; Q1

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14. Coronary Angiography after Cardiac Arrest without ST-Segment Elevation
Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak R, Vlachojannis GJ, Eikemans BJW, van der Harst P, van der Horst ICC, Voskuil M, van der Heijden JJ, Beishuizen A, Stoel M, Camaro C, van der Hoeven H, Henriques JP, Vlaar APJ, Vink MA, van den Bogaard B, Heestermans TACM, de RW, Delnoij TSR, Crijns HJGM, Jessurun GAJ, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, van de Ven PM, Oudemans-van Straaten HM, van Royen N

Background: Ischemic heart disease is a major cause of out-of-hospital cardiac arrest. The role of immediate coronary angiography and percutaneous coronary intervention (PCI) in the treatment of patients who have been successfully

resuscitated after cardiac arrest in the absence of ST-segment elevation myocardial infarction (STEMI) remains uncertain.
Methods: In this multicenter trial, we randomly assigned 552 patients who had cardiac arrest without signs of STEMI to undergo immediate coronary angiography or coronary angiography that was delayed until after neurologic recovery. All patients underwent PCI if indicated. The primary end point was survival at 90 days. Secondary end points included survival at 90 days with good cerebral performance or mild or moderate disability, myocardial injury, duration of catecholamine support, markers of shock, recurrence of ventricular tachycardia, duration of mechanical ventilation, major bleeding, occurrence of acute kidney injury, need for renal-replacement therapy, time to target temperature, and neurologic status at discharge from the intensive care unit.
Results: At 90 days, 176 of 273 patients (64.5%) in the immediate angiography group and 178 of 265 patients (67.2%) in the delayed angiography group were alive (odds ratio, 0.89; 95% confidence interval [CI], 0.62 to 1.27; P = 0.51). The median time to target temperature was 5.4 hours in the immediate angiography group and 4.7 hours in the delayed angiography group (ratio of geometric means, 1.19; 95% CI, 1.04 to 1.36). No significant differences between the groups were found in the remaining secondary end points.
Conclusions: Among patients who had been successfully resuscitated after out-of-hospital cardiac arrest and had no signs of STEMI, a strategy of immediate angiography was not found to be better than a strategy of delayed angiography with respect to overall survival at 90 days. (Funded by the Netherlands Heart Institute and others; COACT Netherlands Trial Register number, NTR4973.).

Gepubliceerd: N Engl J Med 2019 Apr 11;380(15):1397-407
Impact factor: 70.670; Q1

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15. Shorter cryoballoon applications times do effect efficacy but result in less phrenic nerve injury: Results of the randomized 123 study
Molenaar MMD, Timmermans CC, Hesselink T, Scholten MF, Ter Bekke RMA, Luermans JGLM, Brusse-Keizer M, Kraaier K, Ten Haken B, Grandjean JG, Vernooy K, van Opstal JM

Background: The second-generation cryoballoon significantly improves outcome of pulmonary vein isolation (PVI) but may cause more complications than the first generation. Currently, no consensus regarding optimal cryoballoon application time exists. The 123-study aimed to assess the minimal cryoballoon application duration necessary to achieve PVI (primary endpoint) and the effect of application duration on prevention of phrenic nerve injury (PNI).
Methods: Patients <75 years of age with paroxysmal atrial fibrillation, normal PV anatomy, and left atrial size <40 cc/m(2) or <50 mm were randomized to two applications of different duration: "short," "medium," or "long." A total of 222 patients were enrolled, 74 per group.
Results: Duration per application was 105 (101-108), 164 (160-168), and 224 (219-226) s and isolation was achieved in 79, 89, and 90% (P < 0.001) of the PVs after two applications in groups short, medium, and long, respectively. Only for the left PVs, the success rate of the short group was significantly less compared to the medium- and long-duration groups (P < 0.001). PNI during the procedure occurred in 19 PVs

(6.5%) in the medium and in 20 PVs (6.8%) in the long duration groups compared to only five PVs (1.7%) in the short duration group (P < 0.001).
Conclusions: Short cryoballoon ablation application times, less than 2 min, did affect the success for the left PVs but not for the right PVs and resulted in less PNI. A PV tailored approach with shorter application times for the right PVs might be advocated.

Gepubliceerd: Pacing Clin Electrophysiol 2019 May;42(5):508-14
Impact factor: 1.340; Q4

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16. Impact of procedural characteristics on coronary vessel wall healing following implantation of second-generation drug-eluting absorbable metal scaffold in patients with de novo coronary artery lesions: an optical coherence tomography analysis
Ozaki Y, Garcia-Garcia HM, Hideo-Kajita A, Kuku KO, Haude M, Ince H, Abizaid A, Tolg R, Lemos PA, von Birgelen C, Christiansen EH, Wijns W, Escaned J, Dijkstra J, Waksman R

Aims: Second-generation drug-eluting absorbable metal scaffold (DREAMS 2G) is an alternative novel device for treating coronary lesions. However, the relationship between in-scaffold dimensions after implantation of DREAMS 2G and vessel healing and luminal results at follow-up is unknown. The aim of this study is, therefore, to investigate whether the expansion index after implantation of DREAMS 2G as assessed by optical coherence tomography (OCT) impacts late luminal status and healing of the vessel wall.
Methods and results: This study comprises of a total 65 out of 123 patients who were enrolled in the BIOSOLVE-II trial. We assessed both qualitative and quantitative OCT findings and the expansion index of DREAMS 2G after implantation frame by frame using OCT. Expansion index was defined as minimum scaffold area/mean reference lumen area. The over-expansion group was also defined with expansion index >1.0. The total number of analysed frames at post-procedure and 6-month follow-up was 8243 and 8263 frames, respectively. At 6-month follow-up, in-scaffold healing was documented by the reduction of 82% in dissections, 93% in attached intra-luminal mass (ILM), 65% in non-attached ILM, and 76% in jailed side branch. The over-expansion group had significantly greater in-scaffold luminal volume loss (LVL) compared with the non-over-expansion group [over-expansion: 35.0 (18.5-52.1) mm3 vs. non-over-expansion: 21.0 (11.6-37.9) mm3, P = 0.039].
Conclusion: Excellent in vivo healing process after implantation of DREAMS 2G was observed at 6 months. We found that higher expansion indices were associated with higher in-scaffold LVL at 6 months assessed by OCT.

Gepubliceerd: Eur Heart J Cardiovasc Imaging 2019 Aug 1;20(8):916-24
Impact factor: 5.260; Q1

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17. Serial 3-Dimensional Optical Coherence Tomography Assessment of Jailed Side-Branch by Second-Generation Drug-Eluting Absorbable Metal Scaffold (from the BIOSOLVE-II Trial)

Ozaki Y, Garcia-Garcia HM, Hideo-Kajita A, Kuku KO, Haude M, Ince H, Abizaid A, Tolg R, Lemos PA, von Birgelen C, Christiansen EH, Wijns W, Escaned J, Waksman R

Second-generation drug-eluting absorbable metal scaffold (DREAMS 2G) is used for treating coronary lesions. However, the natural history of the jailed side-branch (SB) after DREAMS 2G implantation remains to be elucidated. The aim of this study is to investigate the effect of scaffold struts on jailed SBs as assessed by 3-dimensional (3D) optical coherence tomography (OCT) after implantation of DREAMS 2G. We enrolled the patients who received a DREAMS 2G implantation and where OCT was performed at postprocedure and 12-month follow-up in the BIOSOLVE-II trial. The area of the ostium of jailed SBs and number of compartments divided by scaffold struts were assessed by cut-plane analysis using 3D OCT. A total of 24 patients with 61 jailed SBs were analyzed in this study. The number of compartments was significantly decreased (postprocedure; 1.98 +/- 0.84 vs 12 months; 1.10 +/- 0.30, p <0.001) during the 12 months. Since most of the struts disappeared, the ostium area was increased in 62% of jailed SBs at 12 months, however, not significantly different from postprocedure (postprocedure; 0.74 [0.34 to 1.46] mm(2) vs 12 months; 0.78 [0.41 to 1.68] mm(2), p=0.055). The number of compartments created by scaffold struts and branching angle at postprocedure had no effect on the changes of SB ostium area. DREAMS 2G has a favorable absorption process in the jailed SBs up to 12 months and may be considered as an optional therapy for treating lesions that involve SBs.

Gepubliceerd: Am J Cardiol 2019 Jan 4;123(7):1044-51
Impact factor: 2.843; Q2

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18. Quality of life, depression, and anxiety in patients with a subcutaneous versus transvenous defibrillator system
Pedersen SS, Carter N, Barr C, Scholten M, Lambiase PD, Boersma L, Johansen JB, Theuns DAMJ

Background: Use of the subcutaneous implantable defibrillator (S-ICD) has increased because the device received US Food and Drug Administration approval in 2012, but we still know little about whether the quality of life (QoL) of patients with an S-ICD versus a transvenous ICD (TV-ICD) is comparable. We compared S-ICD patients with TV-ICD patients on QoL, depression, and anxiety up to 12 months' follow-up.
Methods: A matched cohort of S-ICD (N = 167) and TV-ICD patients (N = 167) completed measures on QoL, depression, anxiety, and personality at baseline, 3, 6, and 12 months post implant. Data were analyzed using multivariable modeling with repeated measures.
Results: In adjusted analyses, we found no statistically significant differences between cohorts on physical and mental QoL and depression (all Ps > .05), while S-ICD patients reported lower anxiety than TV-ICD patients (P = 0.0007). Both cohorts experienced improvements in physical and mental QoL and symptoms of depression and anxiety over time (all Ps < .001), primarily between implant and 3 months. These improvements were similar for both cohorts with respect to physical and mental QoL

and anxiety (Ps > .05), while S-ICD patients experienced greater reductions in depressive symptoms (P = .0317).
Conclusion: The QoL and depression levels were similar in patients with an S-ICD and a TV-ICD up to 12 months' follow-up, while S-ICD patients reported lower anxiety levels and a greater reduction in depression over time as compared to TV-ICD patients. This knowledge may be important for patients and clinicians, if the indication for implantation allows both the S-ICD and the TV-ICD, making a choice possible.

Gepubliceerd: Pacing Clin Electrophysiol 2019 Nov 2;42(12):1541-51
Impact factor: 1.340; Q4

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19. Five-year clinical outcomes and intracoronary imaging findings of the COMFORTABLE AMI trial: randomized comparison of biodegradable polymer-based biolimus-eluting stents with bare-metal stents in patients with acute ST-segment elevation myocardial infarction
Raber L, Yamaji K, Kelbaek H, Engstrom T, Baumbach A, Roffi M, von Birgelen C, Taniwaki M, Moschovitis A, Zaugg S, Ostojic M, Pedrazzini G, Karagiannis-Voules DA, Luscher TF, Kornowski R, Tuller D, Vukcevic V, Heg D, Windecker S

Aims: The long-term outcomes of biolimus-eluting stents (BESs) with biodegradable polymer as compared with bare-metal stent (BMS) in patients with ST-segment elevation myocardial infarction (STEMI) remain unknown.
Methods and Results: We performed a 5-year clinical follow-up of 1157 patients (BES: N = 575 and BMS: N = 582) included in the randomized COMFORTABLE AMI trial. Serial intracoronary imaging of stented segments using both intravascular ultrasound (IVUS) and optical coherence tomography performed at baseline and 13 months follow-up were analysed in 103 patients. At 5 years, BES reduced the risk of major adverse cardiac events [MACE; hazard ratio (HR) 0.56, 95% confidence interval (CI): 0.39-0.79, P = 0.001], driven by lower risks for target vessel-related reinfarction (HR 0.44, 95% CI: 0.22-0.87, P = 0.02) and ischaemia-driven target lesion revascularization (HR 0.41, 95% CI: 0.25-0.66, P < 0.001). Definite stent thrombosis (ST) was recorded in 2.2% and 3.9% (HR 0.57, 95% CI: 0.28-1.16, P = 0.12) with no differences in rates of very late definite ST (1.3% vs. 1.6%, P = 0.77). Optical coherence tomography showed no difference in the frequency of malapposed stent struts at follow-up (BES 0.08% vs. BMS 0.02%, P = 0.10). Uncovered stent struts were rarely observed but more frequent in BES (2.1% vs. 0.15%, P < 0.001). In the IVUS analysis, there was no positive remodelling in either group (external elastic membrane area change BES: -0.63 mm2, 95% CI: -1.44 to 0.39 vs. BMS -1.11 mm2, 95% CI: -2.27 to 0.04, P = 0.07).
Conclusion: Compared with BMS, the implantation of biodegradable polymer-coated BES resulted in a lower 5-year rate of MACE in patients with STEMI undergoing primary percutaneous coronary intervention. At 13 months, vascular healing in treated culprit lesions was almost complete irrespective of stent type. CLINICAL
Trial Registration: http://www.clinicaltrials.gov. Unique identifier: NCT00962416.

Gepubliceerd: Eur Heart J 2019 Jun 21;40(24):1909-19
Impact factor: 24.889; Q1

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20. Myocardial fibrosis as an early feature in phospholamban p.Arg14del mutation carriers: phenotypic insights from cardiovascular magnetic resonance imaging

Te Rijdt WP, Ten Sande JN, Gorter TM, van der Zwaag PA, van Rijsingen IA, Boekholdt SM, van Tintelen JP, van Haelst PL, Planken RN, de Boer RA, Suurmeijer AJH, van Veldhuisen DJ, Wilde AAM, Willems TP, van Dessel PFHM, van den Berg MP

Aims: The p.Arg14del founder mutation in the gene encoding phospholamban (PLN) is associated with an increased risk of malignant ventricular arrhythmia (VA) and heart failure. It has been shown to lead to calcium overload, cardiomyocyte damage, and eventually to myocardial fibrosis. This study sought to investigate ventricular function, the extent and localization of myocardial fibrosis and the associations with ECG features and VA in PLN p.Arg14del mutation carriers.
Methods and results: Cardiovascular magnetic resonance (CMR) data of 150 mutation carriers were analysed retrospectively. Left ventricular (LV) and right ventricular (RV) volumes, mass, and ejection fraction were measured. The extent of late gadolinium enhancement (LGE) was expressed as a percentage of myocardial mass. All standard ECG parameters were measured. Occurrence of VA was analysed on ambulatory 24-h and/or exercise electrocardiography, if available. Mean age was 40 +/- 15 years, 42% males, and 7% were index patients while 93% were pre-symptomatic carriers identified after family cascade screening. Mean LV ejection fraction (LVEF) and RV ejection fraction were 58 +/- 9% and 55 +/- 9%, respectively. LV-LGE was present in 91% of mutation carriers with reduced LVEF (<45%) and in 30% of carriers with preserved LVEF. In carriers with positive LV-LGE, its median extent was 5.9% (interquartile range 3.2-12.7). LGE was mainly observed in the inferolateral wall. Carriers with inverted T-waves in the lateral ECG leads more often had LV-LGE ($P < 0.01$) than carriers without. Finally, the presence of LV-LGE, but not attenuated R-waves and inverted lateral T-waves, was independently associated with VA.
Conclusion: LV myocardial fibrosis is present in many PLN p.Arg14del mutation carriers, and who still have a preserved LVEF. It is seen predominantly in the LV inferolateral wall and corresponds with electrocardiographic repolarization abnormalities. Although preliminary, myocardial fibrosis was found to be independently associated with VA. Our findings support the use of CMR with LGE early in the diagnostic work-up.

Gepubliceerd: Eur Heart J Cardiovasc Imaging 2019;20(1):92-100
Impact factor: 5.260; Q1

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21. Predicting Early Mortality Among Implantable Defibrillator Patients Treated With Cardiac Resynchronization Therapy

Theuns DAMJ, Van Boven N, Schaer BA, Hesselink T, Rivero-Ayerza M, Umans V, Sticherling C, Scholten MF, Verbrugge F, Zijlstra F

Background: The beneficial effects of a cardiac resynchronization defibrillator (CRT-D) in patients with heart failure, low left ventricular ejection fraction (LVEF), and wide QRS have clearly been established. Nevertheless, mortality remains high in some

patients. The aim of this study was to develop and validate a risk score to identify patients at high risk for early mortality who are implanted with a CRT-D.
Methods and Results: For predictive modelling, 1282 consecutive patients from 5 centers (74% male; median age 66 years; median LVEF 25%; New York Heart Association class III-IV 60%; median QRS-width 160 ms) were randomly divided into a derivation and validation cohort. The primary endpoint is mortality at 3 years. Model development was performed using multivariate logistic regression by checking log likelihood, Akaike information criterion, and Bayesian information criterion. Model performance was validated using C statistics and calibration plots. The risk score included 7 independent mortality predictors, including myocardial infarction, LVEF, QRS duration, chronic obstructive pulmonary disease, chronic kidney disease, hyponatremia, and anemia. Calibration-in-the-large was suboptimal, reflected by a lower observed mortality (44%) than predicted (50%). The validated C statistic was 0.71 indicating modest performance.
Conclusion: A risk score based on routine, readily available clinical variables can assist in identifying patients at high risk for early mortality within 3 years after CRT-D implantation.

Gepubliceerd: J Card Fail 2019 Oct;25(10):812-8
Impact factor: 3.967; Q2

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22. Evaluation of Microvascular Injury in Revascularized Patients With ST-Segment-Elevation Myocardial Infarction Treated With Ticagrelor Versus Prasugrel

van Leeuwen MAH, van der Hoeven NW, Janssens GN, Everaars H, Nap A, Lemkes JS, de Waard GA, van de Ven PM, van Rossum AC, Ten Cate TJF, Piek JJ, von Birgelen C, Escaned J, Valgimigli M, Diletti R, Riksen NP, Van Mieghem NM, Nijveldt R, van Royen N

Background: Despite successful restoration of epicardial vessel patency with primary percutaneous coronary intervention, coronary microvascular injury occurs in a large proportion of patients with ST-segment-elevation myocardial infarction, adversely affecting clinical and functional outcome. Ticagrelor has been reported to increase plasma adenosine levels, which might have a protective effect on the microcirculation. We investigated whether ticagrelor maintenance therapy after revascularized ST-segment-elevation myocardial infarction is associated with less coronary microvascular injury compared to prasugrel maintenance therapy.
Methods: A total of 110 patients with ST-segment-elevation myocardial infarction received a loading dose of ticagrelor and were randomized to maintenance therapy of ticagrelor (n=56) or prasugrel (n=54) after primary percutaneous coronary intervention. The primary outcome was coronary microvascular injury at 1 month, as determined with the index of microcirculatory resistance in the infarct-related artery. Cardiovascular magnetic resonance imaging was performed during the acute phase and at 1 month.
Results: The primary outcome of index of microcirculatory resistance was not superior in ticagrelor- or prasugrel-treated patients (ticagrelor, 21 [interquartile range, 15-39] U; prasugrel, 18 [interquartile range, 11-29] U; P=0.08). Recovery of microcirculatory resistance over time was not better in patients with ticagrelor versus prasugrel (ticagrelor, -13.9 U; prasugrel, -13.5 U; P=0.96). Intramyocardial

hemorrhage was observed less frequently in patients receiving ticagrelor (23% versus 43%; P=0.04). At 1 month, no difference in infarct size was observed (ticagrelor, 7.6 [interquartile range, 3.7-14.4] g, prasugrel 9.9 [interquartile range, 5.7-16.6] g; P=0.17). The occurrence of microvascular obstruction was not different in patients on ticagrelor (28%) or prasugrel (41%; P=0.35). Plasma adenosine concentrations were not different during the index procedure and during maintenance therapy with ticagrelor or prasugrel.
Conclusions: In patients with ST-segment-elevation myocardial infarction, ticagrelor maintenance therapy was not superior to prasugrel in preventing coronary microvascular injury in the infarct-related territory as assessed by the index of microcirculatory resistance, and this resulted in a comparable infarct size at 1 month. CLINICAL
Trial Registration: URL: https://www.clinicaltrials.gov . Unique identifier: NCT02422888.

Gepubliceerd: Circulation 2019 Jan 29;139(5):636-46
Impact factor: 23.054; Q1

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23. Effect of remote monitoring on patient-reported outcomes in European heart failure patients with an implantable cardioverter-defibrillator: primary results of the REMOTE-CIED randomized trial
Versteeg H, Timmermans I, Widdershoven J, Kimman GJ, Prevot S, Rauwolf T, Scholten MF, Zitron E, Mabo P, Denollet J, Pedersen SS, Meine M

Aims: The European REMOTE-CIED study is the first randomized trial primarily designed to evaluate the effect of remote patient monitoring (RPM) on patient-reported outcomes in the first 2 years after implantation of an implantable cardioverter-defibrillator (ICD).
Methods and Results: The sample consisted of 595 European heart failure patients implanted with an ICD compatible with the Boston Scientific LATITUDE(R) RPM system. Patients were randomized to RPM plus a yearly in-clinic ICD check-up vs. 3-6-month in-clinic check-ups alone. At five points during the 2-year follow-up, patients completed questionnaires including the Kansas City Cardiomyopathy Questionnaire and Florida Patient Acceptance Survey (FPAS) to assess their heart failure-specific health status and ICD acceptance, respectively. Information on clinical status was obtained from patients' medical records. Linear regression models were used to compare scores between groups over time. Intention-to-treat and per-protocol analyses showed no significant group differences in patients' health status and ICD acceptance (subscale) scores (all Ps > 0.05). Exploratory subgroup analyses indicated a temporary improvement in device acceptance (FPAS total score) at 6-month follow-up for secondary prophylactic in-clinic patients only (P < 0.001). No other significant subgroup differences were observed.
Conclusion: Large clinical trials have indicated that RPM can safely and effectively replace most in-clinic check-ups of ICD patients. The REMOTE-CIED trial results show that patient-reported health status and ICD acceptance do not differ between patients on RPM and patients receiving in-clinic check-ups alone in the first 2 years after ICD implantation.ClinicalTrials.gov Identifier: NCT01691586.

Gepubliceerd: Europace 2019 Sep 1;21(9):1360-8

Impact factor: 5.047; Q1

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24. Superiority of biodegradable polymer sirolimus-eluting stents in STEMI
von Birgelen C, Buiten RA

Lancet 2019 Oct 5;394(10205):1208-10
Impact factor: 59.102; Q1

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25. Effectiveness of the European Society of Cardiology/Heart Failure Association website 'heartfailurematters.org' and an e-health adjusted care pathway in patients with stable heart failure: results of the 'e-Vita HF' randomized controlled trial
Wagenaar KP, Broekhuizen BDL, Jaarsma T, Kok I, Mosterd A, Willems FF, Linssen GCM, Agema WRP, Anneveldt S, Lucas CMHB, Mannaerts HFJ, Wajon EMCJ, Dickstein K, Cramer MJ, Landman MAJ, Hoes AW, Rutten FH

Background: Efficient incorporation of e-health in patients with heart failure (HF) may enhance health care efficiency and patient empowerment. We aimed to assess the effect on self-care of (i) the European Society of Cardiology/Heart Failure Association website 'heartfailurematters.org' on top of usual care, and (ii) an e-health adjusted care pathway leaving out 'in person' routine HF nurse consultations in stable HF patients.
Methods and Results: In a three-group parallel-randomized trial in stable HF patients from nine Dutch outpatient clinics, we compared two interventions (heartfailurematters.org website and an e-health adjusted care pathway) to usual care. The primary outcome was self-care measured with the European Heart Failure Self-care Behaviour Scale. Secondary outcomes were health status, mortality, and hospitalizations. In total, 450 patients were included. The mean age was 66.8 +/- 11.0 years, 74.2% were male, and 78.8% classified themselves as New York Heart Association I or II at baseline. After 3 months of follow-up, the mean score on the self-care scale was significantly higher in the groups using the website and the adjusted care pathway compared to usual care (73.5 vs. 70.8, 95% confidence interval 0.6-6.2; and 78.2 vs. 70.8, 95% confidence interval 3.8- 9.4, respectively). The effect attenuated, until no differences after 1 year between the groups. Quality of life showed a similar pattern. Other secondary outcomes did not clearly differ between the groups.
Conclusions: Both the heartfailurematters.org website and an e-health adjusted care pathway improved self-care in HF patients on the short term, but not on the long term. Continuous updating of e-health facilities could be helpful to sustain effects.
CLINICAL
Trial Registration: ClinicalTrials.gov ID NCT01755988.

Gepubliceerd: Eur J Heart Fail 2019;21(2):238-46
Impact factor: 12.129; Q1

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26. Simultaneous evaluation of plaque stability and ischemic potential of coronary lesions in a fluid-structure interaction analysis

Wu X, von Birgelen C, Zhang S, Ding D, Huang J, Tu S

The measurement of fractional flow reserve (FFR) and superficial wall stress (SWS) identifies inducible myocardial ischemia and plaque vulnerability, respectively. A simultaneous evaluation of both FFR and SWS is still lacking, while it may have a major impact on therapy. A new computational model of one-way fluid-structure interaction (FSI) was implemented and used to perform a total of 54 analyses in virtual coronary lesion models, based on plaque compositions, arterial remodeling patterns, and stenosis morphologies under physiological conditions. Due to a greater lumen dilation and more induced strain, FFR in the lipid-rich lesions (0.81 +/- 0.15) was higher than that in fibrous lesions (0.79 +/- 0.16, P = 0.001) and calcified lesions (0.79 +/- 0.16, P = 0.001). Four types of lesions were further defined, based on the combination of cutoff values for FFR (0.80) and maximum relative SWS (30 kPa): The level of risk increased from (1) plaques with mild-to-moderate stenosis but negative remodeling for lipid-rich (Type A: non-ischemic, stable) to (2) lipid-rich plaques with mild-to-moderate stenosis and without-to-positive remodeling (Type B: non-ischemic, unstable) or plaques with severe stenosis but negative remodeling for lipid-rich (Type C: ischemic, stable) to (3) lipid-rich plaques with severe stenosis and without-to-positive remodeling (Type D: ischemic, unstable). The analysis of FSI to simultaneously evaluate inducible myocardial ischemia and plaque stability may be useful to identify coronary lesions at a high risk and to ultimately optimize treatment. Further research is warranted to assess whether a more aggressive treatment may improve the prognosis of patients with non-ischemic, intermediate, and unstable lesions.

Gepubliceerd: Int J Cardiovasc Imaging 2019 Sep;35(9):1563-72
Impact factor: 1.860; Q3

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27. Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation
Pluymaekers NAHA, Dudink EAMP, Luermans JGLM, Meeder JG, Lenderink T, Widdershoven J, Bucx JJJ, Rienstra M, Kamp O, van Opstal JM, Alings M, Oomen A, Kirchhof CJ, Van Dijk VF, Ramanna H, Liem A, Dekker LR, Essers BAB, Tijssen JGP, Van Gelder IC, Crijns HJGM

Background: Patients with recent-onset atrial fibrillation commonly undergo immediate restoration of sinus rhythm by pharmacologic or electrical cardioversion. However, whether immediate restoration of sinus rhythm is necessary is not known, since atrial fibrillation often terminates spontaneously.
Methods: In a multicenter, randomized, open-label, noninferiority trial, we randomly assigned patients with hemodynamically stable, recent-onset (<36 hours), symptomatic atrial fibrillation in the emergency department to be treated with a wait-and-see approach (delayed-cardioversion group) or early cardioversion. The wait-and-see approach involved initial treatment with rate-control medication only and delayed cardioversion if the atrial fibrillation did not resolve within 48 hours. The primary end point was the presence of sinus rhythm at 4 weeks. Noninferiority would be shown if the lower limit of the 95% confidence interval for the between-group difference in the primary end point in percentage points was more than -10.
Results: The presence of sinus rhythm at 4 weeks occurred in 193 of 212 patients (91%) in the delayed-cardioversion group and in 202 of 215 (94%) in the early-

cardioversion group (between-group difference, -2.9 percentage points; 95% confidence interval [CI], -8.2 to 2.2; P = 0.005 for noninferiority). In the delayed-cardioversion group, conversion to sinus rhythm within 48 hours occurred spontaneously in 150 of 218 patients (69%) and after delayed cardioversion in 61 patients (28%). In the early-cardioversion group, conversion to sinus rhythm occurred spontaneously before the initiation of cardioversion in 36 of 219 patients (16%) and after cardioversion in 171 patients (78%). Among the patients who completed remote monitoring during 4 weeks of follow-up, a recurrence of atrial fibrillation occurred in 49 of 164 patients (30%) in the delayed-cardioversion group and in 50 of 171 (29%) in the early-cardioversion group. Within 4 weeks after randomization, cardiovascular complications occurred in 10 patients and 8 patients, respectively.
Conclusions: In patients presenting to the emergency department with recent-onset, symptomatic atrial fibrillation, a wait-and-see approach was noninferior to early cardioversion in achieving a return to sinus rhythm at 4 weeks. (Funded by the Netherlands Organization for Health Research and Development and others; RACE 7 ACWAS ClinicalTrials.gov number, NCT02248753.).

Gepubliceerd: N Engl J Med 2019 Apr 18;380(16):1499-508
Impact factor: 70.670; Q1

Totale impact factor: 397.28
Gemiddelde impact factor: 14.714

Aantal artikelen 1e, 2e of laatste auteur: 7
Totale impact factor: 89.702
Gemiddelde impact factor: 12.82

Dermatologie

1. A rare case with prominent features of both discoid lupus erythematosus and pemphigus foliaceus
Bilgic Temel A., Ergun E, Poot AM, Bassorgun CI, Akman-Karakas A, Uzun S, Alpsoy E, Pas HH, Jonkman MF

Gepubliceerd: J Eur Acad Dermatol Venereol 2019 Jan;33(1):e5-e7
Impact factor: 5.113; Q1

Totale impact factor: 5.113
Gemiddelde impact factor: 5.113

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

Gynaecologie

1. Underestimation of pelvic organ prolapse in the supine straining position, based on magnetic resonance imaging findings
Grob ATM, Olde Heuvel J, Futterer JJ, Massop D, Veenstra van Nieuwenhoven AL, Simonis FFJ, van der Vaart CH

Objective: Pelvic organ prolapse (POP) is clinically diagnosed in the supine position, where the effect of gravity is simulated by having the patients put strain on their pelvic floor. The objective of this study was to determine the degree of POP underestimation in the supine position based on magnetic resonance imaging (MRI) findings.
Methods: This prospective study was conducted with symptomatic POP grade >/= 2 patients. Fifteen female patients were examined with an MRI system that allows supine and upright imaging. The differences between supine and upright in distances of the bladder neck, cervix, and pouch of Douglas from the pubococcygeal line (PCL) were estimated, together with changes in the genital hiatal area. Patients were scanned at rest and during straining. All distances were compared using the Wilcoxon ranking test.
Results: All mean distances from the PCL increased from the supine-strain to the upright-rest and from the supine-strain to the upright-strain position. These distances were found in the supine and upright positions: the bladder descended 1.3 cm to 1.4 cm, the cervix 1.1 cm to 2.2 cm, and the pouch of Douglas 0.8 cm to 1.5 cm respectively (all p values <0.05). The hiatal area was larger in the upright-strain position (mean 42.0 cm(2); SD +/-14.8) than during the supine-strain position (mean 33.5 cm(2); SD +/-14.5), with a p value of 0.02.
Conclusion: Upright MRI scanning of patients with POP grade >/= 2 both at rest and during straining shows a significantly larger extent of the prolapse than that observed during supine straining.

Gepubliceerd: Int Urogynecol J 2019 Nov;30(11):1939-44
Impact factor: 2.094; Q2

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2. Determinants of successful lifestyle change during a 6-month preconception lifestyle intervention in women with obesity and infertility
Karsten MDA, van Oers AM, Groen H, Mutsaerts MAQ, van Poppel MNM, Geelen A, van de Beek C, Painter RC, Mol BWJ, Roseboom TJ, Hoek A

Purpose: To identify demographic, (bio)physical, behavioral, and psychological determinants of successful lifestyle change and program completion by performing a secondary analysis of the intervention arm of a randomized-controlled trial, investigating a preconception lifestyle intervention.
Methods: The 6-month lifestyle intervention consisted of dietary counseling, physical activity, and behavioral modification, and was aimed at 5-10% weight loss. We operationalized successful lifestyle change as successful weight loss (>/= 5% weight/BMI </= 29 kg/m(2)), weight loss in kilograms, a reduction in energy intake, and an increase in physical activity during the intervention program. We performed

logistic and mixed-effect regression analyses to identify baseline factors that were associated with successful change or program completion.
Results: Women with higher external eating behavior scores had higher odds of successful weight loss (OR 1.10, 95% CI 1.05-1.16). Women with the previous dietetic support lost 0.94 kg less during the intervention period (95% CI 0.01-1.87 kg). Women with higher self-efficacy reduced energy intake more than women with lower self-efficacy ($p < 0.01$). Women with an older partner had an increased energy intake (6 kcal/year older, 95% CI 3-13). A high stage of change towards physical activity was associated with a higher number of daily steps ($p = 0.03$). A high stage of change towards weight loss was associated with completion of the intervention ($p = 0.04$).
Conclusions: Determinants of lifestyle change and program completion were: higher external eating behavior, not having received previous dietetic support, high stage of change. This knowledge can be used to identify women likely to benefit from lifestyle interventions and develop new interventions for women requiring alternative support.
Trial Registration: The LIFEstyle study was registered at the Dutch trial registry (NTR 1530; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1530).

Gepubliceerd: Eur J Nutr 2019 Sep;58(6):2463-75
Impact factor: 4.449; Q1

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3. Cesarean scar pregnancy
Kleijweg AMM, Veenstra-van Nieuwenhoven AL, Sikkema JM, Halbesma JR, Alhafidh AHH

Background: A rare, but potentially life-threatening complication of a Cesarean section is a so-called Cesarean scar pregnancy (CSP). This concerns an ectopic pregnancy, where the implantation takes place in a niche of the Cesarean section scar.
Case description: We describe the case of a 29-year-old pregnant woman (G5P3), who after a amenorrhoea period of 6 weeks was referred to us by a midwife because the sonography showed an empty uterus. She had previously undergone two Cesarean sections. During transvaginal sonography we observed a small amiotic sac in the Cesarean section scar, lacking a clear heart rhythm.
Conclusion: Since there are no general guidelines for the treatment of CSP, a patient-specific approach should be taken to determine optimal management. There is, however, a clear preference to terminate the pregnancy as soon as possible.

Gepubliceerd: Ned Tijdschr Geneeskd 2019 Apr 11;163:1876-8784
Impact factor: 0; nvt

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4. Evaluation of effectiveness of the PlasmaJet surgical device in the treatment of advanced stage ovarian cancer (PlaComOv-study): study protocol of a randomized controlled trial in the Netherlands
Nieuwenhuyzen-de Boer GM, Hofhuis W, Reesink-Peters N, Ewing-Graham PC, Schoots IG, Beltman JJ, Piek JMJ, Baalbergen A, Kooi GS, van Haaften A, van Huisseling H, Haans L, Dorman M, van Beekhuizen HJ

Background: The most important goal for survival benefit of advanced stage ovarian cancer is to surgically remove all visible tumour, because complete cytoreductive surgery (CCS) has been shown to be associated with prolonged survival. In a remarkable number of women, CCS is very challenging. Especially in women with many small metastases on the peritoneum and intestinal surface, conventional CCS with electrosurgery is not able to be "complete" in removing safely all visible tumour. In this randomized controlled trail (RCT) we investigate whether the use of the PlasmaJet Surgical Device increases the rate of CCS, and whether this indeed leads to a longer progression free and overall survival. The main research question is: does the use of the PlasmaJet Surgical Device in surgery for advanced stage ovarian cancer result in an increased number of complete cytoreductive surgeries when compared with conventional surgical techniques. Secondary study objectives are: 30-day morbidity, duration of surgery, blood loss, length of hospitalisation, Quality of Life, disease-free survival, overall survival, percentage colostomy, cost-effectiveness.
Methods: The study design is a multicentre single-blinded superiority RCT in two university and nine non-university hospitals in The Netherlands. Three hundred and thirty women undergoing cytoreductive surgery for advanced stage ovarian carcinoma (FIGO Stage IIIB-IV) will be randomized into two arms: use of the PlasmaJet (intervention group) versus the use of standard surgical instruments combined with electrocoagulation (control group). The primary outcome is the rate of complete cytoreductive surgery in both groups. Secondary study objectives are: 30-day morbidity, duration of surgery, blood loss, length of hospitalisation, Quality of Life, disease-free survival, overall survival, percentage colostomy, cost-effectiveness. Quality of life will be evaluated using validated questionnaires at baseline, at 1 and 6 months after surgery and at 1, 2, 3 and 4 years after surgery.
Discussion: We hypothesize the additional value of the use of the PlasmaJet in CCS for advanced stage epithelial ovarian cancer. More knowledge about efficacy, side effects, recurrence rates, cost effectiveness and pathology findings after using the PlasmaJet Device is advocated. This RCT may aid in this void.
Trial Registration: Dutch Trial Register NTR6624 . Registered 18 August 2017.

Gepubliceerd: BMC Cancer 2019 Jan 14;19(1):58
Impact factor: 2.933; Q3

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5. Evaluation of two vaginal, uterus sparing operations for pelvic organ prolapse: modified Manchester operation (MM) and sacrospinous hysteropexy (SSH), a study protocol for a multicentre randomized non-inferiority trial (the SAM study)

Schulten SFM, Enklaar RA, Kluivers KB, van Leijsen SAL, Jansen-van der Weide MC, Adang EMM, van Bavel J, van Dongen H, Gerritse MBE, van Gestel I, Malmberg GGA, Mouw RJC, van Rumpt-van de Geest DA, Spaans WA, van der Steen A, Stekelenburg J, Tiersma ESM, Verkleij-Hagoort AC, Vollebregt A, Wingen CBM, Weemhoff M, van Eijndhoven HWF

Background: Pelvic organ prolapse (POP) affects up to 40% of parous women which adversely affects the quality of life. During a life time, 20% of all women will undergo an operation. In general the guidelines advise a vaginal operation in case of uterine descent: hysterectomy with uterosacral ligament plication (VH), sacrospinous hysteropexy (SSH) or a modified Manchester operation (MM). In the last decade,

renewed interest in uterus sparing techniques has been observed. Previous studies have shown non-inferiority between SSH and VH. Whether or not SSH and MM are comparable concerning anatomical and functional outcome is still unknown. The practical application of both operations is at least in The Netherlands a known cause of practice pattern variation (PPV). To reveal any difference between both techniques the SAM-study was designed.
Methods: The SAM-study is a randomized controlled multicentre non-inferiority study which compares SSH and MM. Women with symptomatic POP in any stage, uterine descent and POP-Quantification (POP-Q) point D at </= minus 1 cm are eligible. The primary outcome is the composite outcome at two years of absence of prolapse beyond the hymen in any compartment, the absence of bulge symptoms and absence of reoperation for pelvic organ prolapse. Secondary outcomes are hospital parameters, surgery related morbidity/complications, pain perception, further treatments for prolapse or urinary incontinence, POP-Q anatomy in all compartments, quality-of-life, sexual function, and cost-effectiveness. Follow-up takes place at 6 weeks, 12 and 24 months. Additionally at 12 weeks, 6 and 9 months cost-effectiveness will be assessed. Validated questionnaires will be used and gynaecological examination will be performed. Analysis will be performed following the intention-to-treat and per protocol principle. With a non-inferiority margin of 9% and an expected loss to follow-up of 10%, 424 women will be needed to prove non-inferiority with a confidence interval of 95%.
Discussion: This study will evaluate the effectiveness and costs of SSH versus MM in women with primary POP. The evidence will show whether the existing PPV is detrimental and a de-implementation process regarding one of the operations is needed.
Trial Registration: Dutch Trial Register (NTR 6978, http://www.trialregister.nl).

Gepubliceerd: BMC Womens Health 2019 Apr 2;19(1):49
Impact factor: 1.592; Q3

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6. The capacity of transvaginal hydrolaparoscopy versus hysterosalpingography to diagnose tubal pathology in the work-up of subfertile women, a randomised clinical trial
Tros R, van Kessel MA, van Kuijk SMJ, Oosterhuis GJE, Kuchenbecker WKH, Kwee J, Bongers MY, Mol BWJ, Koks CAM

Objective: To assess the capacity of transvaginal hydrolaparoscopy (THL) versus hysterosalpingography (HSG) as a primary tool to diagnose tubal pathology. STUDY
Design: We performed a multicenter RCT (NTR3462) in 4 teaching hospitals in the Netherlands, comparing THL and HSG as first line tubal test in subfertile women. The primary outcome of the trial was cumulative live birth rate at 24 months. Here, we present the secondary outcomes, the diagnostic findings of both THL and HSG as well as performance defined as failures, complications and pain- and acceptability scores.
Results: Between May 2013 and October 2016, we allocated 149 women to THL and 151 to HSG, of which 17 women in the THL group (11.4%) and 12 in the HSG group (7.9%) conceived naturally before the scheduled procedure, while 13 HSGs and 5 THLs were not performed for other reasons (withdrawal of informed consent, not willing to undergo tubal testing and protocol violations). A total of 119 THLs and 134

HSGs were carried out. Failures were seen more in the THL group (n = 8, 5.6%) than in the HSG group (n = 1, 0.7%) (p = 0.014). Complications did not differ significantly between the groups (THL n = 4; 2.8% vs HSG n = 1; 0.7%) (p = 0.20). Bilateral tubal occlusion was detected in one versus three women (0.9% versus 2.2%) of the THL group and HSG group, while unilateral tubal occlusion was detected in seven (6.2%) versus eight (5.9%) women, respectively. Normal findings were seen in 96 (79.3%) women randomised to THL and in 119 (87.5%) in women randomised for HSG (RR 0.91 95%CI 0.81-1.01, p = 0.08). The pain score was significantly less for THL (VAS 4.7 (SD: 2.5)) than for HSG (VAS 5.4 (SD:2.5)) (p 0.038). The acceptability rate of THL and was high and comparable.
Conclusion: THL and HSG have a comparable capacity in diagnosing tubal pathology with comparable performance in safety, pain and acceptability.

Gepubliceerd: Eur J Obstet Gynecol Reprod Biol 2019 May;236:127-32
Impact factor: 2.024; Q3

Totale impact factor: 13.092
Gemiddelde impact factor: 2.182

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 6.473
Gemiddelde impact factor: 2.158

Heelkunde

1. Second and third look laparoscopy in pT4 colon cancer patients for early detection of peritoneal metastases; the COLOPEC 2 randomized multicentre trial

Bastiaenen VP, Klaver CEL, Kok NFM, de Wilt JHW, de Hingh IHJT, Aalbers AGJ, Boerma D, Bremers AJA, Burger JWA, van Duyn EB, Evers P, van Grevenstein WMU, Hemmer PHJ, Madsen EVE, Snaebjornsson P, Tuynman JB, Wiezer MJ, Dijkgraaf MGW, van der Bilt JDW, Tanis PJ

Background: Approximately 20-30% of patients with pT4 colon cancer develop metachronous peritoneal metastases (PM). Due to restricted accuracy of imaging modalities and absence of early symptoms, PM are often detected at a stage in which only a quarter of patients are eligible for curative intent treatment. Preliminary findings of the COLOPEC trial (NCT02231086) revealed that PM were already detected during surgical re-exploration within two months after primary resection in 9% of patients with pT4 colon cancer. Therefore, second look diagnostic laparoscopy (DLS) to detect PM at a subclinical stage may be considered an essential component of early follow-up in these patients, although this needs confirmation in a larger patient cohort. Furthermore, a third look DLS after a negative second look DLS might be beneficial for detection of PM occurring at a later stage.
Methods: The aim of this study is to determine the yield of second look DLS and added value of third look DLS after negative second look DLS in detecting occult PM in pT4N0-2 M0 colon cancer patients after completion of primary treatment. Patients will undergo an abdominal CT at 6 months postoperative, followed by a second look DLS within 1 month if no PM or other metastases not amenable for local treatment are detected. Patients without PM will subsequently be randomized between routine follow-up including 18 months abdominal CT, or an experimental arm with a third look DLS provided that PM or incurable metastases are absent at the 18 months abdominal CT. Primary endpoint is the proportion of PM detected after a negative second look DLS and will be determined at 20 months postoperative.
Discussion: Second look DLS is supposed to result in 10% occult PM, and third look DLS after negative second look DLS is expected to detect an additional 10% of PM compared to routine follow-up alone in patients with pT4 colon cancer. Detection of PM at an early stage will likely increase the proportion of patients eligible for curative intent treatment and subsequently improve survival, given the uniformly reported direct association between the extent of peritoneal disease and survival.
Trial Registration: ClinicalTrials.gov: NCT03413254 , January 2018.

Gepubliceerd: BMC Cancer 2019 Mar 21;19(1):254
Impact factor: 2.933; Q3

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2. A steady decline in pancreas transplantation rates

Benjamens S, Leemkuil M, Margreiter C, Huurman VA, Leuvenink HG, Pol RA

Background/Objectives: After years of growth in many pancreas transplant programs, UNOS has reported declining transplant numbers in the USA. This

precipitating trend urges for an evaluation of the transplant numbers and scientific productivity in the Eurotransplant region and the UK.
Methods: We performed a trend analysis of pancreas transplantation rates, between 1997 and 2016, adjusting for changes in population size, and an analysis of scientific publications in this field. We used information from the UNOS, Eurotransplant, and UK transplant registry and bibliometric information from the Web of Science database.
Results: Between 2004 and 2016 there was an average annual decline in pancreas transplantation rates per million inhabitants of 3.3% in the USA and 2.5% in the Eurotransplant region. In the UK, transplant numbers showed an average annual decline of 1.0% from 2009 to 2016. Publications in Q1 journals showed an annual change of -2.1% and +20.1%, before 2004, and a change of -3.8% and -5.5%, between 2004 and 2016, for USA and Eurotransplant publications, respectively.
Conclusions: Adjusting pancreas transplantation rates for changes in population size showed a clear decline in transplant numbers in both the USA and Eurotransplant region, with first signs of decline in the UK. Following this trend, the number of scientific publications in this field have declined worldwide.

Gepubliceerd: Pancreatology 2019 Jan;19(1):31-8
Impact factor: 3.241; Q2

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3. Pancreas transplantation in patient with long-standing diabetes mellitus: How to judge fitness for transplant?
Benjamens S, Leemkuil M, Pol RA

Gepubliceerd: Clin Transplant 2019 Nov;33(11):e13726
Impact factor: 1.667; Q3

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4. Patient's Skeletal Muscle Radiation Attenuation and Sarcopenic Obesity are Associated with Postoperative Morbidity after Neoadjuvant Chemoradiation and Resection for Rectal Cancer
Berkel AEM, Klaase JM, de Graaff F, Brusse-Keizer MGJ, Bongers BC, van Meeteren NLU

Background/Aims: To investigate the relation between skeletal muscle measurements (muscle mass, radiation attenuation, and sarcopenic obesity), postoperative morbidity, and survival after treatment of locally advanced rectal cancer.
Methods: This explorative retrospective study identified 99 consecutive patients who underwent neoadjuvant chemoradiation and surgery between January 2007 and May 2012. Skeletal muscle mass was measured as total psoas area and total abdominal muscle area (TAMA) at 3 anatomical levels using the patient's preoperative computed tomography scan. Radiation attenuation was measured using corresponding mean Hounsfield units for TAMA. Sarcopenic obesity was defined as body mass index above 25 kg.m-2 combined with skeletal muscle mass index below the sex-specific median. Postoperative complications were graded by using the -Clavien-Dindo classification.

Results: Twenty-five patients (25.3%) developed a grade 3-5 complication. Lower radiation attenuation was independently associated with overall ($p = 0.003$) and grade 3-5 complications ($p = 0.002$). Sarcopenic obesity was associated with overall complications (all $p < 0.05$). Skeletal muscle measurements and survival were not significantly related.
Conclusion: Radiation attenuation was associated with overall and grade 3-5 postoperative morbidity after neoadjuvant chemoradiation and non-laparoscopic resection for rectal cancer. Sarcopenic obesity was associated with overall complications.

Gepubliceerd: Dig Surg 2019;36(5):376-83
Impact factor: 1.884; Q2

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5. The Impact of Revascularisation on Quality of Life in Chronic Mesenteric Ischemia
Blauw JTM, Pastoors HAM, Brusse-Keizer M, Beuk RJ, Kolkman JJ, Geelkerken RH, For The Dutch Mesenteric Ischemia Study Group

Background: Chronic mesenteric ischemia (CMI) is characterized by long-standing abdominal symptoms due to insufficient mesenteric circulation. Data on the effect of revascularisation on quality of life (QoL) for CMI are scarce. This study is the first to evaluate the impact of revascularisation on quality of life.
Methods: Seventy-nine patients with CMI or acute-on-chronic mesenteric ischemia (AoCMI) underwent an intervention of one or more mesenteric arteries between January 2010 and July 2012. QoL before and after intervention was measured with the EuroQol-5D. Preintervention questionnaires were of standard care. Postintervention data were obtained by resending a questionnaire to the patients between February and May 2013. To investigate the clinical relevance of our findings, the minimal clinically important difference (MCID) was used. Since there is no established MCID for CMI, we used the literature reference MCID of inflammatory bowel syndrome (IBS) of 0.074.
Results: Fifty-five (69.6%) of 79 patients returned their questionnaire and 23 (29.1%) were completely filled out. There was a significant increase of the median EQ-index score from 0.70 to 0.81 ($p=0.02$) and a significant reduction of symptoms in the domains usual activities (34.4%) and pain/discomfort (32.3%). There was a significant improvement of 17% in overall current health condition (VAS) ($p=0.001$). The MCID between baseline and postoperative EQ-5D index score was 0.162, indicating a clinically relevant improvement of quality of life after revascularisation.
Conclusion: Quality of life of CMI patients is improved after mesenteric artery revascularisation.

Gepubliceerd: Can J Gastroenterol Hepatol 2019;2019:7346013
Impact factor: 1.714; Q4

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6. Possible Preventable Causes of Unplanned Readmission After Elective Liver Resection, Results from a Non-academic Referral HPB Center
de Klein GW, Brohet RM, Liem MSL, Klaase JM

Introduction: Unplanned readmission is a common event after liver resection, and it is a burden for both patients and healthcare policy makers. This study evaluates the incidence of and reasons for unplanned readmission after liver resection, in order to identify possible preventable causes.
Methods: In this single-center cohort study, data from patients who underwent liver resection for both malignant and benign indications from 2001 to 2016 at our institute were collected from a database with prospective data. Readmissions were analyzed for their reasons and risk factors. Patients with general complaints with no specific complications were categorized as failure to thrive.
Results: In 406 patients, the readmission rate was 11.6%. Most patients were readmitted because of failure to thrive (35%), deep and superficial surgical site infection (28%), or cardiopulmonary complications (15%). A multivariate analysis revealed that unplanned readmission was associated with the occurrence of complications during index admission-with an odds ratio of 4.69 (CI 2.41-9.12, $p < 0.001$).
Conclusion: Readmission occurs in more than 1 in 10 patients after liver resection, and it is associated with a complicated course during index admission. One-third of readmissions occur because of failure to thrive and might be preventable. Future research in strategies to reduce readmission rates should focus on both the prevention of complications during index admission and programs at the interface between primary and secondary care.

Gepubliceerd: World J Surg 2019 Jul;43(7):1802-8
Impact factor: 2.768; Q2

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7. Early results with the custom-made Fenestrated Anaconda aortic cuff in the treatment of complex abdominal aortic aneurysm
de Niet A, Reijnen MMPJ, Zeebregts CJ, Fenestrated Anaconda Cuff Study Group, includes Meerwaldt R, Geelkerken RH

Objective: The objective of this study was to investigate the feasibility of a specific custom-made fenestrated aortic cuff in the treatment of complex abdominal aortic aneurysms (AAAs).
Methods: Between 2013 and 2016, a total of 57 custom-made Fenestrated Anaconda (Vascutek, Inchinnan, Scotland, UK) aortic cuffs were placed in 38 centers worldwide. All centers were invited to participate in this retrospective analysis. Postoperative and follow-up data included the presence of adverse events, necessity for reintervention, and renal function.
Results: Fifteen clinics participated, leading to 29 cases. Median age at operation was 74 years (interquartile range [IQR], 71-78 years); five patients were female. Two patients were treated for a para-anastomotic AAA after open AAA repair, 19 patients were treated because of a complicated course after primary endovascular AAA repair, and 8 cases were primary procedures for AAA. A total of 76 fenestrations (mean, 2.6 per case) were used. Four patients needed seven adjunctive procedures. Two patients underwent conversion, one because of a dissection of the superior mesenteric artery and one because of perforation of a renal artery. Median operation time was 225 minutes (IQR, 150-260 minutes); median blood loss, 200 mL (IQR, 100-500 mL); and median contrast volume, 150 mL (IQR, 92-260 mL). Primary technical success was achieved in 86% and secondary technical success in 93%. The 30-day

morbidity was 7 of 29 with a mortality rate of 4 of 29. Estimated glomerular filtration rate remained unchanged before and after surgery (76 to 77 mL/min/m(2)). Between preoperative and median follow-up of 11 months, estimated glomerular filtration rate was reduced statistically significantly (76 to 63 mL/min/m(2)). During follow-up, 9 cases had an increase in aneurysm sac diameter (5 cases >5 mm); 14 cases had a stable or decreased aneurysm sac diameter; and in 2 cases, no aneurysm size was reported. No type I endoleak was reported, and two cases with a type III endoleak were treated by endovascular means during follow-up. Survival, reintervention-free survival, and target vessel patency at 1 year were 81% +/- 8%, 75% +/- 9%, and 99% +/- 1%, respectively. After 2 years, these numbers were 81% +/- 8%, 67% +/- 11%, and 88% +/- 6%, respectively. During follow-up, the two patients with a type III endoleak needed endograft-related reinterventions.
Conclusions: Treatment with this specific custom-made fenestrated aortic cuff is feasible after complicated previous (endovascular) aortic repair or in complex AAAs. The complexity of certain AAA cases is underlined in this study, and the Fenestrated Anaconda aortic cuff is a valid option in selected cases in which few treatment options are left.

Gepubliceerd: J Vasc Surg 2019 Feb;69(2):348-56
Impact factor: 3.243; Q1

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8. Minimally Invasive Versus Open Distal Pancreatectomy (LEOPARD): A Multicenter Patient-blinded Randomized Controlled Trial
de Rooij T, van Hilst J, van Santvoort H, Boerma D, van den Boezem P, Daams F, van Dam R, Dejong C, van Duyn E, Dijkgraaf M, van Eijck C, Festen S, Gerhards M, Groot Koerkamp B, de Hingh I, Kazemier G, Klaase J, de Kleine R, van Laarhoven C, Luyer M, Patijn G, Steenvoorde P, Suker M, Abu Hilal M, Busch O, Besselink M

Objective: This trial followed a structured nationwide training program in minimally invasive distal pancreatectomy (MIDP), according to the IDEAL framework for surgical innovation, and aimed to compare time to functional recovery after minimally invasive and open distal pancreatectomy (ODP).
Background: MIDP is increasingly used and may enhance postoperative recovery as compared with ODP, but randomized studies are lacking.
Methods: A multicenter patient-blinded randomized controlled superiority trial was performed in 14 centers between April 2015 and March 2017. Adult patients with left-sided pancreatic tumors confined to the pancreas without vascular involvement were randomly assigned (1:1) to undergo MIDP or ODP. Patients were blinded for type of surgery using a large abdominal dressing. The primary endpoint was time to functional recovery. Analysis was by intention to treat. This trial was registered with the Netherlands Trial Register (NTR5689).
Results: Time to functional recovery was 4 days [interquartile range (IQR) 3-6) in 51 patients after MIDP versus 6 days (IQR 5-8) in 57 patients after ODP (P < 0.001). The conversion rate of MIDP was 8%. Operative blood loss was less after MIDP (150 vs 400 mL; P < 0.001), whereas operative time was longer (217 vs 179 minutes; P = 0.005). The Clavien-Dindo grade >/=III complication rate was 25% versus 38% (P = 0.21). Delayed gastric emptying grade B/C was seen less often after MIDP (6% vs 20%; P = 0.04). Postoperative pancreatic fistulas grade B/C were seen in 39% after MIDP versus 23% after ODP (P = 0.07), without difference in percutaneous catheter

drainage (22% vs 20%; P = 0.77). Quality of life (day 3-30) was better after MIDP as compared with ODP, and overall costs were non-significantly less after MIDP. No 90-day mortality was seen after MIDP versus 2% (n = 1) after ODP.
Conclusions: In patients with left-sided pancreatic tumors confined to the pancreas, MIDP reduces time to functional recovery compared with ODP. Although the overall rate of complications was not reduced, MIDP was associated with less delayed gastric emptying and better quality of life without increasing costs.

Gepubliceerd: Ann Surg 2019;269(1):2-9
Impact factor: 9.476; Q1

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9. Outcomes of a Multicenter Training Program in Laparoscopic Pancreatoduodenectomy (LAELAPS-2)
de Rooij T, van Hilst J, Topal B, Bosscha K, Brinkman DJ, Gerhards MF, de Hingh IH, Karsten TM, Lips DJ, Luyer MD, Marsman HA, van Rijssen LB, Steen MW, Busch OR, Festen S, Besselink MG

Objective: The aim of the study was to assess feasibility and outcomes of a multicenter training program in laparoscopic pancreatoduodenectomy (LPD).
Background: Whereas expert centers have reported promising outcomes of LPD, nationwide analyses have raised concerns on its safety, especially during the learning curve. Multicenter, structured LPD training programs reporting outcomes including the first procedures are lacking. No LPD had been performed in the Netherlands before this study.
Methods: During 2014-2016, 8 surgeons from 4 high-volume centers completed the Longitudinal Assessment and Realization of Laparoscopic Pancreatic Surgery (LAELAPS-2) training program in LPD, including detailed technique description, video training, and proctoring. In all centers, LPD was performed by 2 surgeons with extensive experience in pancreatic and laparoscopic surgery. Outcomes of all LPDs were prospectively collected.
Results: In total, 114 patients underwent LPD. Median pancreatic duct diameter was 3 mm [interquartile range (IQR = 2-4)] and pancreatic texture was soft in 74% of patients. The conversion rate was 11% (n = 12), median blood loss 350 mL (IQR = 200-700), and operative time 375 minutes (IQR = 320-431). Grade B/C postoperative pancreatic fistula occurred in 34% of patients, requiring catheter drainage in 22% and re-operation in 2%. A Clavien-Dindo grade >/= III complication occurred in 43% of patients. Median length of hospital stay was 15 days (IQR = 9-25). Overall, 30-day and 90-day mortality were both 3.5%. Outcomes were similar for the first and second part of procedures.
Conclusions: This LPD training program was feasible and ensured acceptable outcomes during the learning curve in all centers. Future studies should determine whether such a training program is applicable in other settings and assess the added value of LPD.

Gepubliceerd: Ann Surg 2019 Feb;269(2):344-50
Impact factor: 9.476; Q1

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10. Electronic Health Program to Empower Patients in Returning to Normal Activities After General Surgical and Gynecological Procedures: Intervention Mapping as a Useful Method for Further Development

den Bakker CM, Schaafsma FG, van der Meij E, Meijerink WJ, van den Heuvel B, Baan AH, Davids PH, Scholten PC, van der Meij S, van Baal WM, van Dalsen AD, Lips DJ, van der Steeg JW, Leclercq WK, Geomini PM, Consten EC, Schraffordt Koops SE, de Castro SM, van Kesteren PJ, Cense HA, Stockmann HB, Ten Cate AD, Bonjer HJ, Huirne JA, Anema JR

Background: Support for guiding and monitoring postoperative recovery and resumption of activities is usually not provided to patients after discharge from the hospital. Therefore, a perioperative electronic health (eHealth) intervention ("ikherstel" intervention or "I recover" intervention) was developed to empower gynecological patients during the perioperative period. This eHealth intervention requires a need for further development for patients who will undergo various types of general surgical and gynecological procedures.
Objective: This study aimed to further develop the "ikherstel" eHealth intervention using Intervention Mapping (IM) to fit a broader patient population.
Methods: The IM protocol was used to guide further development of the "ikherstel" intervention. First, patients' needs were identified using (1) the information of a process evaluation of the earlier performed "ikherstel" study, (2) a review of the literature, (3) a survey study, and (4) focus group discussions (FGDs) among stakeholders. Next, program outcomes and change objectives were defined. Third, behavior change theories and practical tools were selected for the intervention program. Finally, an implementation and evaluation plan was developed.
Results: The outcome for an eHealth intervention tool for patients recovering from abdominal general surgical and gynecological procedures was redefined as "achieving earlier recovery including return to normal activities and work." The Attitude-Social Influence-Self-Efficacy model was used as a theoretical framework to transform personal and external determinants into change objectives of personal behavior. The knowledge gathered by needs assessment and using the theoretical framework in the preparatory steps of the IM protocol resulted in additional tools. A mobile app, an activity tracker, and an electronic consultation (eConsult) will be incorporated in the further developed eHealth intervention. This intervention will be evaluated in a multicenter, single-blinded randomized controlled trial with 18 departments in 11 participating hospitals in the Netherlands.
Conclusions: The intervention is extended to patients undergoing general surgical procedures and for malignant indications. New intervention tools such as a mobile app, an activity tracker, and an eConsult were developed.
Trial Registration: Netherlands Trial Registry NTR5686; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5686¶

Gepubliceerd: J Med Internet Res 2019 Feb 6;21(2):e9938
Impact factor: 4.945; Q1

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11. Cross-Sectional Study on MRI Restaging After Chemoradiotherapy and Interval to Surgery in Rectal Cancer: Influence on Short- and Long-Term Outcomes

Detering R, Borstlap WAA, Broeders L, Hermus L, Marijnen CAM, Beets-Tan RGH, Bemelman WA, van Westreenen HL, Tanis PJ, Dutch Snapshot Research Group,includes Lips DJ

Background: The time interval between CRT and surgery in rectal cancer patients is still the subject of debate. The aim of this study was to first evaluate the nationwide use of restaging magnetic resonance imaging (MRI) and its impact on timing of surgery, and, second, to evaluate the impact of timing of surgery after chemoradiotherapy (CRT) on short- and long-term outcomes.
Methods: Patients were selected from a collaborative rectal cancer research project including 71 Dutch centres, and were subdivided into two groups according to time interval from the start of preoperative CRT to surgery (< 14 and >/= 14 weeks).
Results: From 2095 registered patients, 475 patients received preoperative CRT. MRI restaging was performed in 79.4% of patients, with a median CRT-MRI interval of 10 weeks (interquartile range [IQR] 8-11) and a median MRI-surgery interval of 4 weeks (IQR 2-5). The CRT-surgery interval groups consisted of 224 (< 14 weeks) and 251 patients (>/= 14 weeks), and the long-interval group included a higher proportion of cT4 stage and multivisceral resection patients. Pathological complete response rate (n = 34 [15.2%] vs. n = 47 [18.7%], p = 0.305) and CRM involvement (9.7% vs. 15.9%, p = 0.145) did not significantly differ. Thirty-day surgical complications were similar (20.1% vs. 23.1%, p = 0.943), however no significant differences were found for local and distant recurrence rates, disease-free survival, and overall survival.
Conclusions: These real-life data, reflecting routine daily practice in The Netherlands, showed substantial variability in the use and timing of restaging MRI after preoperative CRT for rectal cancer, as well as time interval to surgery. Surgery before or after 14 weeks from the start of CRT resulted in similar short- and long-term outcomes.

Gepubliceerd: Ann Surg Oncol 2019 Feb;26(2):437-48
Impact factor: 3.681; Q1

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12. pH-responsive materials for optical monitoring of wound status
Gamerith C, Luschnig D, Ortner A, Pietrzik N, Guse JH, Burnet M, Haalboom M, van der Palen J, Heinzle A, Sigl E, Gübitz GM

The monitoring of infection status of wounds is an emerging field and the pH of wound exudate is considered one potential indicator of infection. pH indicators intended for use in medical devices, such as swabs or dressings, need to be fixed in place, however, visual pH indicators are usually soluble molecules so are not inherently suitable for use in devices. To address this, we developed a rapid and simple immobilisation method for coupling pH-responsive dyes onto solid phases. The use of a silane based coupling agent for immobilisation of bromocresol purple led to a shift in the pH dependent spectral properties of the resulting material. The pH responsive material changes from yellow to green to blue with rising pH providing an ideal contrast to the reddish colour of most wound exudates. This is a key advantage over currently available alternatives when considering the suitability of this material for incorporation into various medical devices. In addition, we analysed clinical study samples to verify the association between wound infection and elevated pH-values. A

device with an embedded indicator that changes to a contrast colour could represent a simple and easy-to-use system for detecting wounds at risk of infection..

Gepubliceerd: Sensors and Actuators B: Chemical 2019;301:126966
Impact factor: 6.393; Q1

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13. Computer aided quantification of intratumoral stroma yields an independent prognosticator in rectal cancer
Geessink OGF, Baidoshvili A, Klaase JM, Ehteshami Bejnordi B, Litjens GJS, van Pelt GW, Mesker WE, Nagtegaal ID, Ciompi F, van der Laak JAWM

Purpose: Tumor-stroma ratio (TSR) serves as an independent prognostic factor in colorectal cancer and other solid malignancies. The recent introduction of digital pathology in routine tissue diagnostics holds opportunities for automated TSR analysis. We investigated the potential of computer-aided quantification of intratumoral stroma in rectal cancer whole-slide images.
Methods: Histological slides from 129 rectal adenocarcinoma patients were analyzed by two experts who selected a suitable stroma hot-spot and visually assessed TSR. A semi-automatic method based on deep learning was trained to segment all relevant tissue types in rectal cancer histology and subsequently applied to the hot-spots provided by the experts. Patients were assigned to a 'stroma-high' or 'stroma-low' group by both TSR methods (visual and automated). This allowed for prognostic comparison between the two methods in terms of disease-specific and disease-free survival times.
Results: With stroma-low as baseline, automated TSR was found to be prognostic independent of age, gender, pT-stage, lymph node status, tumor grade, and whether adjuvant therapy was given, both for disease-specific survival (hazard ratio = 2.48 (95% confidence interval 1.29-4.78)) and for disease-free survival (hazard ratio = 2.05 (95% confidence interval 1.11-3.78)). Visually assessed TSR did not serve as an independent prognostic factor in multivariate analysis.
Conclusions: This work shows that TSR is an independent prognosticator in rectal cancer when assessed automatically in user-provided stroma hot-spots. The deep learning-based technology presented here may be a significant aid to pathologists in routine diagnostics.

Gepubliceerd: Cell Oncol (Dordr) 2019 Jun;42(3):331-41
Impact factor: 5.020; Q1

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14. Culture results from wound biopsy versus wound swab: does it matter for the assessment of wound infection?
Haalboom M, Blokhuis-Arkes MHE, Beuk RJ, Meerwaldt R, Klont R, Schijffelen MJ, Bowler PB, Burnet M, Sigl E, van der Palen JAM

Objectives: The aim of this study was to determine whether assessment of wound infection differs when culture results from wound biopsy versus wound swab are available in clinical practice.
Methods: For 180 eligible patients, a swab and biopsy were taken from one wound during a regular appointment at a wound care facility in eastern Netherlands. Culture

results from both methods were supplemented with clinical information and provided to a panel of six experts who independently assessed each wound as infect or not, separately for swab and biopsy. Assessments for biopsy and swab were compared for the complete expert panel, and for individual experts.
Results: The complete expert panel provided the same wound assessment based on (clinical information and) culture results from wound biopsy and wound swab in 158 of 180 wounds (87.8%, kappa 0.67). For individual experts, agreement between biopsy and swab varied between 77% and 96%. However, there were substantial differences between experts: the same assessment was provided in 62 (34.4%) to 76 (42.2%) wounds for swab and biopsy respectively.
Conclusions: Assessment of infection does not significantly differ when culture results from swabs or biopsies are available. The substantial variability between individual experts indicates non-uniformity in the way wounds are assessed. This complicates accurate detection of infection and comparability between studies using assessment of infection as reference standard.

Gepubliceerd: Clin Microbiol Infect 2019;25(5):629.e7-629.e12
Impact factor: 6.425; Q1

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15. Differentiation between infected and non-infected wounds using an electronic nose
Haalboom M, Gerritsen JW, van der Palen J

Objectives: The aim of this study was to explore whether an electronic nose, Aetholab, is able to discriminate between infected versus non-infected wounds, based on headspace analyses from wound swabs.
Methods: A total of 77 patients participated in this pilot study. Each wound was assessed for infection based on clinical judgment. Additionally, two wound swabs were taken, one for microbiological culture and one for measurement with Aetholab. Diagnostic properties with 95% confidence intervals (95%CIs) of Aetholab were calculated with clinical judgment and microbiological culture results as reference standards.
Results: With clinical judgment as reference standard, Aetholab had a sensitivity of 91% (95%CI 76-98) and a specificity of 71% (95%CI 55-84). Diagnostic properties were somewhat lower when microbiological culture results were used as reference standard: sensitivity 81% (95%CI 64-91), specificity 63% (95%CI 46-77).
Conclusions: Aetholab seems a promising diagnostic tool for wound infection given the diagnostic properties presented in this pilot study. A larger study is needed to confirm our results.

Gepubliceerd: Clin Microbiol Infect 2019 Oct;25(10):1288
Impact factor: 6.425; Q1

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16. Superiority of Step-up Approach vs Open Necrosectomy in Long-term Follow up of Patients With Necrotizing Pancreatitis
Hollemans RA, Bakker OJ, Boermeester MA, Bollen TL, Bosscha K, Bruno MJ, Buskens E, Dejong CH, van Duijvendijk P, van Eijck CH, Fockens P, van Goor H, van Grevenstein WM, van der Harst E, Heisterkamp J, Hesselink EJ, Hofker S, Houdijk

AP, Karsten T, Kruyt PM, van Laarhoven CJ, Lameris JS, van Leeuwen MS, Manusama ER, Molenaar IQ, Nieuwenhuijs VB, van Ramshorst B, Roos D, Rosman C, Schaapherder AF, van der Schelling GP, Timmer R, Verdonk RC, de Wit RJ, Gooszen HG, Besselink MG, van Santvoort HC

Background and aims: In a 2010 randomized trial (the PANTER trial), a surgical step-up approach for infected necrotizing pancreatitis was found to reduce the composite endpoint of death or major complications compared with open necrosectomy; 35% of patients were successfully treated with simple catheter drainage only. There is concern, however, that minimally invasive treatment increases the need for reinterventions for residual peripancreatic necrotic collections and other complications during the long term. We therefore performed a long-term follow-up study.
Methods: We re-evaluated all the 73 patients (of the 88 patients randomly assigned to groups) who were still alive after the index admission, at a mean 86 months (+/-11 months) follow up. We collected data on all clinical and health care resource utilization endpoints through this follow-up period. The primary endpoint was death or major complications (the same as for the PANTER trial). We also measured exocrine insufficiency, quality of life (using the SF-36 and EQ-5D forms) and Izbicki pain scores.
Results: From index admission to long-term follow up, 19 patients (44%) died or had major complications in the step-up group compared with 33 patients (73%) in the open-necrosectomy group (P=.005). Significantly lower proportions of patients in the step-up group had incisional hernias (23% vs 53%; P=.004), pancreatic exocrine insufficiency (29% vs 56%; P=.03), or endocrine insufficiency (40% vs 64%; P=.05). There were no significant differences between groups in proportions of patients requiring additional drainage procedures (11% vs 13%; P=.99) or pancreatic surgery (11% vs 5%; P=.43), or in recurrent acute pancreatitis, chronic pancreatitis, Izbicki pain-scores, or medical costs. Quality of life increased during follow up without a significant difference between groups.
Conclusions: In an analysis of long-term outcomes of trial participants, we found the step-up approach for necrotizing pancreatitis to be superior to open necrosectomy, without increased risk of reinterventions.

Gepubliceerd: Gastroenterology 2019;156(4):1016-26
Impact factor: 19.809; Q1

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17. Outcomes of Resectability Assessment of the Dutch Colorectal Cancer Group Liver Metastases Expert Panel
Huiskens J, Bolhuis K, Engelbrecht MR, de Jong KP, Kazemier G, Liem MS, Verhoef C, de Wilt JH, Punt CJ, van Gulik TM

Background: Decision making on optimal treatment strategy in patients with initially unresectable colorectal cancer liver metastases (CRLM) remains complex because uniform criteria for (un)resectability are lacking. This study reports on the feasibility and short-term outcomes of The Dutch Colorectal Cancer Group Liver Expert Panel.
STUDY
Design: The Expert Panel consists of 13 hepatobiliary surgeons and 4 radiologists. Resectability assessment is performed independently by 3 randomly assigned

surgeons, and CRLM are scored as resectable, potentially resectable, or permanently unresectable. In absence of consensus, 2 additional surgeons are invited for a majority consensus. Patients with potentially resectable or unresectable CRLM at baseline are evaluated every 2 months of systemic therapy. Once CRLM are considered resectable, a treatment strategy is proposed.
Results: Overall, 398 panel evaluations in 183 patients were analyzed. The median time to panel conclusion was 7 days (interquartile range [IQR] 5-11 days). Intersurgeon disagreement was observed in 205 (52%) evaluations, with major disagreement (resectable vs permanently unresectable) in 42 (11%) evaluations. After systemic treatment, 106 patients were considered to have resectable CRLM, 84 of whom (79%) underwent a curative procedure. R0 resection (n = 41), R0 resection in combination with ablative treatment (n = 26), or ablative treatment only (n = 4) was achieved in 67 of 84 (80%) patients.
Conclusions: This study analyzed prospective resectability evaluation of patients with CRLM by a panel of radiologists and liver surgeons. The high rate of disagreement among experienced liver surgeons reflects the complexity in defining treatment strategies for CRLM and supports the use of a panel rather than a single-surgeon decision.

Gepubliceerd: J Am Coll Surg 2019 Dec;229(6):523-32
Impact factor: 4.450; Q1

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18. Spontaneous regression of a sporadic intra-abdominal located desmoid-type fibromatosis
Kloeze J, van Veen M
Background: Desmoid-type fibromatosis (DTF) is a rare benign proliferation of myofibroblasts with an unpredictable disease course. Treatment of intra-abdominal located DTF is difficult because of the close relationship with vital organs.
Case presentation: A healthy young male presents with an asymptomatic palpable mass in the lower right abdominal quadrant. A computed tomography shows a 10 x 7 cm(2) pear-shaped mass, and pathological examination revealed DTF. A watchful waiting approach was initiated, as the patient was asymptomatic and surgery would imply a significant amount of intestinal resection. After a follow-up of 2 years, the tumor has regressed spontaneously and the patient is still without symptoms.
Conclusions: DTF is a difficult to treat condition where individualized management is appropriate. An asymptomatic patient could be treated with a watchful waiting approach, even with intra-abdominal location. Thereby sparing unnecessary morbidity as the tumor can be stable for many years or even regress spontaneously.

Gepubliceerd: J Surg Case Rep 2019 Feb;2019(2):rjz037
Impact factor: 0; nvt

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19. Geometric Remodeling of the Perirenal Aortic Neck at and Adjacent to the Double Sealing Ring of the Anaconda Stent-Graft After Endovascular Aneurysm Repair
Koenrades MA, Bosscher MRF, Ubbink JT, Slump CH, Geelkerken RH

Purpose: To evaluate if the radial force of the double sealing ring of the Anaconda stent-graft induces dilatation in the perirenal aortic neck adjacent to the rings. Materials and
Methods: This study evaluated the serial electrocardiogram-gated computed tomography scans of 15 abdominal aortic aneurysm patients (mean age 72.8+/-3.7 years; 14 men) who were treated electively using an Anaconda stent-graft. Follow-up scans were conducted before discharge and at 1, 6, 12, and 24 months after endovascular repair. Diameter and area were assessed perpendicular to the aortic centerline along the perirenal aortic neck, which was subdivided into 3 zones: the suprastent, the stent, and the infrastent zones. Measurements were performed independently by 2 experienced observers using dedicated 3-dimensional image processing software.
Results: Between discharge and the 2-year follow-up the diameter and area remained stable in the suprastent zone [average diameter change: -0.1+/-0.4 mm (-0.4%+/-1.7%), p=0.893; average area change: -2.9+/-17.2 mm(2) (-0.7%+/-3.4%), p=0.946], increased in the stent zone [average diameter change: +1.9+/-1.0 mm (+7.3%+/-4.0%), p<0.001; average area change: +84.3+/-48.3 mm(2) (+15.5%+/-8.7%), p<0.001], and diverged in the infrastent zone [average diameter change: -0.8+/-2.2 mm (-2.3%+/-7.4%), p>0.99; average area change: -34.6+/-102.3 mm(2) (-4.1%+/-14.8%), p>0.99; increased in 4 patients, decreased in 9 patients].
Conclusion: After Anaconda implantation the infrarenal aortic neck accommodated to the expansion of the sealing rings at the stent zone. Below the stent zone the neck diameter decreased in the majority of patients, while an increase was related to downstream displacement of the main body. A decrease in size in the infrastent zone may contribute to durable sealing and fixation. A personalized follow-up scheme based on geometric neck remodeling should be feasible if our observations are confirmed in larger, long-term studies.

Gepubliceerd: J Endovasc Ther 2019 Dec;26(6):855-64
Impact factor: 2.986; Q1

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20. Quantitative Stent Graft Motion in ECG Gated CT by Image Registration and Segmentation: In Vitro Validation and Preliminary Clinical Results
Koenrades MA, Struijs EM, Klein A, Kuipers H, Reijnen MMPJ, Slump CH, Geelkerken RH

Objectives: The dynamic endovascular environment of stent grafts may influence long term outcome after endovascular aneurysm repair (EVAR). The sealing and fixation of a stent graft to the aortic wall is challenged at every heartbeat, yet knowledge of the cardiac induced dynamics of stent grafts is sparse. Understanding the stent-artery interaction is crucial for device development and may aid the prediction of failure in the individual patient. The aim of this work was to establish quantitative stent graft motion in multiphasic electrocardiogram (ECG) gated computed tomography (CT) by image registration and segmentation techniques.
Methods: Experimental validation was performed by evaluating a series of ECG gated CT scans of a stent graft moving at different amplitudes of displacement at different virtual heart rates using a motion generating device with synchronised ECG triggering. The methodology was further tested on clinical data of patients treated with EVAR devices with different stent graft designs. Displacement during the cardiac

cycle was analysed for points on the fixating stent rings, the branches or fenestrations, and the spine.
Results: Errors for the amplitude of displacement measured in vitro at individual points on the wire frame were at most 0.3 mm. In situ cardiac induced displacement of the devices was found to differ per location and also depended on the type of stent graft. Displacement during the cardiac cycle was greatest in a fenestrated device and smallest in a chimney graft sac anchoring endosystem, with maximum displacement varying from 0.0 to 1.4 mm. There was no substantial displacement measurable in the spine.
Conclusions: A novel methodology to quantify and visualise stent graft motion in multiphasic ECG gated CT has been validated in vitro and tested in vivo. This methodology enables further exploration of in situ motion of different stent grafts and branch stents and their interaction with native vessels.

Gepubliceerd: Eur J Vasc Endovasc Surg 2019 Nov;58(5):746-55
Impact factor: 3.642; Q1

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21. Pancreas Transplantation from Donors after Circulatory Death: an Irrational Reluctance?
Leemkuil M, Leuvenink HGD, Pol RA

Purpose of review: Beta-cell replacement is the best therapeutic option for patients with type 1 diabetes. Because of donor scarcity, more extended criteria donors are used for transplantation. Donation after circulatory death donors (DCD) are not commonly used for pancreas transplantation, because of the supposed higher risk of complications. This review gives an overview on the pathophysiology, risk factors, and outcome in DCD transplantation and discusses different preservation methods.
Recent findings: Studies on outcomes of DCD pancreata show similar results compared with those of donation after brain death (DBD), when accumulation of other risk factors is avoided. Hypothermic machine perfusion is shown to be a safe method to improve graft viability in experimental settings. DCD should not be the sole reason to decline a pancreas for transplantation. Adequate donor selection and improved preservation techniques can lead to enhanced pancreas utilization and outcome.

Gepubliceerd: Curr Diab Rep 2019 Nov 18;19(11):129
Impact factor: 3.996; Q2

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22. Alternative Fistula Risk Score for Pancreatoduodenectomy (a-FRS): Design and International External Validation
Mungroop TH, van Rijssen LB, van Klaveren D, Smits FJ, van Woerden V, Linnemann RJ, de Pastena M, Klompmaker S, Marchegiani G, Ecker BL, van Dieren S, Bonsing B, Busch OR, van Dam RM, Erdmann J, van Eijck CH, Gerhards MF, van Goor H, van der Harst E, de Hingh IH, de Jong KP, Kazemier G, Luyer M, Shamali A, Barbaro S, Armstrong T, Takhar A, Hamady Z, Klaase J, Lips DJ, Molenaar IQ, Nieuwenhuijs VB, Rupert C, van Santvoort HC, Scheepers JJ, van der Schelling GP, Bassi C, Vollmer CM, Steyerberg EW, Abu Hilal M, Groot Koerkamp B, Besselink MG

Objective: The aim of this study was to develop an alternative fistula risk score (a-FRS) for postoperative pancreatic fistula (POPF) after pancreatoduodenectomy, without blood loss as a predictor.
Background: Blood loss, one of the predictors of the original-FRS, was not a significant factor during 2 recent external validations.
Methods: The a-FRS was developed in 2 databases: the Dutch Pancreatic Cancer Audit (18 centers) and the University Hospital Southampton NHS. Primary outcome was grade B/C POPF according to the 2005 International Study Group on Pancreatic Surgery (ISGPS) definition. The score was externally validated in 2 independent databases (University Hospital of Verona and University Hospital of Pennsylvania), using both 2005 and 2016 ISGPS definitions. The a-FRS was also compared with the original-FRS.
Results: For model design, 1924 patients were included of whom 12% developed POPF. Three predictors were strongly associated with POPF: soft pancreatic texture [odds ratio (OR) 2.58, 95% confidence interval (95% CI) 1.80-3.69], small pancreatic duct diameter (per mm increase, OR: 0.68, 95% CI: 0.61-0.76), and high body mass index (BMI) (per kg/m increase, OR: 1.07, 95% CI: 1.04-1.11). Discrimination was adequate with an area under curve (AUC) of 0.75 (95% CI: 0.71-0.78) after internal validation, and 0.78 (0.74-0.82) after external validation. The predictive capacity of a-FRS was comparable with the original-FRS, both for the 2005 definition (AUC 0.78 vs 0.75, P = 0.03), and 2016 definition (AUC 0.72 vs 0.70, P = 0.05).
Conclusion: The a-FRS predicts POPF after pancreatoduodenectomy based on 3 easily available variables (pancreatic texture, duct diameter, BMI) without blood loss and pathology, and was successfully validated for both the 2005 and 2016 POPF definition.

Gepubliceerd: Ann Surg 2019;269(5):937-43
Impact factor: 9.476; Q1

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23. Incidence and Treatment of Limb Occlusion of the Anaconda Endograft After Endovascular Aneurysm Repair
Rodel SGJ, Zeebregts CJ, Meerwaldt R, van der Palen J, Geelkerken RH

Purpose: To evaluate the incidence and treatment of limb occlusions of the second- and third-generation Anaconda endografts.
Methods: A single-center retrospective study was conducted involving 317 consecutive patients (mean age 76 years; 289 men) who underwent endovascular aneurysm repair for elective asymptomatic, symptomatic intact, and ruptured infrarenal abdominal aortic aneurysm with 2 versions of the Anaconda device. From September 2003 to July 2011, the second-generation device was used in 189 patients (mean age 77 years; 169 men) and from July 2011 to September 2015, the third-generation device was implanted in 128 patients (mean age 75 years; 120 men). The rates of limb occlusion were compared between groups and according to compliance with the instructions for use (IFU); predictors were sought in multivariate analysis. The results of the latter are given as the hazard ratio (HR) and 95% confidence interval (CI).
Results: Kaplan-Meier freedom of occlusion estimates for second- and third-generation devices, respectively, was 96.6% and 95.0% at 1 year, 89.9% and 95.0% at 2 years, and 86.5% and 88.6% at 5 years. There was no significant difference in

overall occlusion rate between the second-generation devices (p=0.332) or with regard to use within the IFU (p=0.827); however, there was a clinically relevant decrease in the occlusion rate for elective patients treated with the third-generation device (6.4% vs 13.1%, p=0.077). There was an increase in the occlusion rate when the iliac limb diameter was </=13 mm. In multivariate analysis, the only independent predictor of limb occlusion was a small distal prosthesis diameter (HR 0.732, 95% CI 0.63 to 0.86, p<0.001). Symptomatic nonruptured and ruptured abdominal aortic aneurysm (AAA) interventions had an almost 2-fold increased risk of occlusion (HR 1.95, 95% CI 0.93 to 4.11, p=0.078), though this did not reach statistical significance. **Conclusion:** The Anaconda design has proven effectiveness in AAA exclusion in daily practice inside the IFU. However, efforts could be made to further reduce the limb occlusion rate.

Gepubliceerd: J Endovasc Ther 2019 Feb;26(1):113-20
Impact factor: 2.986; Q1

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24. Perioperative systemic therapy and cytoreductive surgery with HIPEC versus upfront cytoreductive surgery with HIPEC alone for isolated resectable colorectal peritoneal metastases: protocol of a multicentre, open-label, parallel-group, phase II-III, randomised, superiority study (CAIRO6)

Rovers KP, Bakkers C, Simkens GAAM, Burger JWA, Nienhuijs SW, Creemers GM, Thijs AMJ, Brandt-Kerkhof ARM, Madsen EVE, Ayez N, de Boer NL, van Meerten E, Tuynman JB, Kusters M, Sluiter NR, Verheul HMW, van der Vliet HJ, Wiezer MJ, Boerma D, Wassenaar ECE, Los M, Hunting CB, Aalbers AGJ, Kok NFM, Kuhlmann KFD, Boot H, Chalabi M, Kruijff S, Been LB, van Ginkel RJ, de Groot DJA, Fehrmann RSN, de Wilt JHW, Bremers AJA, de Reuver PR, Radema SA, Herbschleb KH, van Grevenstein WMU, Witkamp AJ, Koopman M, Haj Mohammad N, van Duyn EB, Mastboom WJB, Mekenkamp LJM, Nederend J, Lahaye MJ, Snaebjornsson P, Verhoef C, van Laarhoven HWM, Zwinderman AH, Bouma JM, Kranenburg O, van 't Erve I, Fijneman RJA, Dijkgraaf MGW, Hemmer PHJ, Punt CJA, Tanis PJ, de Hingh IHJT

Background: Upfront cytoreductive surgery with HIPEC (CRS-HIPEC) is the standard treatment for isolated resectable colorectal peritoneal metastases (PM) in the Netherlands. This study investigates whether addition of perioperative systemic therapy to CRS-HIPEC improves oncological outcomes.
Methods: This open-label, parallel-group, phase II-III, randomised, superiority study is performed in nine Dutch tertiary referral centres. Eligible patients are adults who have a good performance status, histologically or cytologically proven resectable PM of a colorectal adenocarcinoma, no systemic colorectal metastases, no systemic therapy for colorectal cancer within six months prior to enrolment, and no previous CRS-HIPEC. Eligible patients are randomised (1:1) to perioperative systemic therapy and CRS-HIPEC (experimental arm) or upfront CRS-HIPEC alone (control arm) by using central randomisation software with minimisation stratified by a peritoneal cancer index of 0-10 or 11-20, metachronous or synchronous PM, previous systemic therapy for colorectal cancer, and HIPEC with oxaliplatin or mitomycin C. At the treating physician's discretion, perioperative systemic therapy consists of either four 3-weekly neoadjuvant and adjuvant cycles of capecitabine with oxaliplatin (CAPOX), six 2-weekly neoadjuvant and adjuvant cycles of 5-fluorouracil/leucovorin with

oxaliplatin (FOLFOX), or six 2-weekly neoadjuvant cycles of 5-fluorouracil/leucovorin with irinotecan (FOLFIRI) followed by four 3-weekly (capecitabine) or six 2-weekly (5-fluorouracil/leucovorin) adjuvant cycles of fluoropyrimidine monotherapy. Bevacizumab is added to the first three (CAPOX) or four (FOLFOX/FOLFIRI) neoadjuvant cycles. The first 80 patients are enrolled in a phase II study to explore the feasibility of accrual and the feasibility, safety, and tolerance of perioperative systemic therapy. If predefined criteria of feasibility and safety are met, the study continues as a phase III study with 3-year overall survival as primary endpoint. A total of 358 patients is needed to detect the hypothesised 15% increase in 3-year overall survival (control arm 50%; experimental arm 65%). Secondary endpoints are surgical characteristics, major postoperative morbidity, progression-free survival, disease-free survival, health-related quality of life, costs, major systemic therapy related toxicity, and objective radiological and histopathological response rates.
Discussion: This is the first randomised study that prospectively compares oncological outcomes of perioperative systemic therapy and CRS-HIPEC with upfront CRS-HIPEC alone for isolated resectable colorectal PM.
Trial Registration: Clinicaltrials.gov/ NCT02758951 , NTR/ NTR6301 , ISRCTN/ ISRCTN15977568 , EudraCT/ 2016-001865-99.

Gepubliceerd: BMC Cancer 2019 Apr 25;19(1):390
Impact factor: 2.933; Q3

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25. Resection of hepatic and pulmonary metastasis from metastatic esophageal and gastric cancer: a nationwide study
Seesing MFJ, van der Veen A, Brenkman HJF, Stockmann HBAC, Nieuwenhuijzen GAP, Rosman C, van den Wildenberg FJH, van Berge MI, van Duijvendijk P, Wijnhoven BPL, Stoot JHMB, Lacle M, Ruurda JP, van Hillegersberg R, Baas PC, Boerma D, de Steur WO, de Waard JWD, Heisterkamp J, van Hillo M, Kouwenhoven EA, Liem MSL, van der Peet DL, Pierie JPEN, Plukker JTM, Roumen RMH, Tetteroo GWM, van Workum F

The standard of care for gastroesophageal cancer patients with hepatic or pulmonary metastases is best supportive care or palliative chemotherapy. Occasionally, patients can be selected for curative treatment instead. This study aimed to evaluate patients who underwent a resection of hepatic or pulmonary metastasis with curative intent. The Dutch national registry for histo- and cytopathology was used to identify these patients. Data were retrieved from the individual patient files. Kaplan-Meier survival analysis was performed. Between 1991 and 2016, 32,057 patients received a gastrectomy or esophagectomy for gastroesophageal cancer in the Netherlands. Of these patients, 34 selected patients received a resection of hepatic metastasis (n = 19) or pulmonary metastasis (n = 15) in 21 different hospitals. Only 4 patients received neoadjuvant therapy before metastasectomy. The majority of patients had solitary, metachronous metastases. After metastasectomy, grade 3 (Clavien-Dindo) complications occurred in 7 patients and mortality in 1 patient. After resection of hepatic metastases, the median potential follow-up time was 54 months. Median overall survival (OS) was 28 months and the 1-, 3-, and 5- year OS was 84%, 41%, and 31%, respectively. After pulmonary metastases resection, the median potential follow-up time was 80 months. The median OS was not reached and the 1-, 3-, and 5-year OS was 67%, 53%, and 53%, respectively. In selected patients with

gastroesophageal cancer with hepatic or pulmonary metastases, metastasectomy was performed with limited morbidity and mortality and offered a 5-year OS of 31-53%. Further prospective studies are required.

Gepubliceerd: Dis Esophagus 2019 Apr 25;32(12)
Impact factor: 2.323; Q3

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26. Protocol for a prospective, longitudinal cohort study on the effect of arterial disease level on the outcomes of supervised exercise in intermittent claudication: the ELECT Registry
van den Houten MM, Jansen SC, Sinnige A, van der Laan L, Vriens PW, Willigendael EM, Lardenoije JH, Elshof JM, van Hattum ES, Lijkwan MA, Nyklicek I, Rouwet EV, Koelemay MJ, Scheltinga MR, Teijink JA

Introduction: Despite guideline recommendations advocating conservative management before invasive treatment in intermittent claudication, early revascularisation remains widespread in patients with favourable anatomy. The aim of the Effect of Disease Level on Outcomes of Supervised Exercise in Intermittent Claudication Registry is to determine the effect of the location of stenosis on the outcomes of supervised exercise in patients with intermittent claudication due to peripheral arterial disease.
Methods and analysis: This multicentre prospective cohort study aims to enrol 320 patients in 10 vascular centres across the Netherlands. All patients diagnosed with intermittent claudication (peripheral arterial disease: Fontaine II/Rutherford 1-3), who are considered candidates for supervised exercise therapy by their own physicians are appropriate to participate. Participants will receive standard care, meaning supervised exercise therapy first, with endovascular or open revascularisation in case of insufficient effect (at the discretion of patient and vascular surgeon). For the primary objectives, patients are grouped according to anatomical characteristics of disease (aortoiliac, femoropopliteal or multilevel disease) as apparent on the preferred imaging modality in the participating centre (either duplex, CT angiography or magnetic resonance angiography). Changes in walking performance (treadmill tests, 6 min walk test) and quality of life (QoL; Vascular QoL Questionnaire-6, WHO QoL Questionnaire-Bref) will be compared between groups, after multivariate adjustment for possible confounders. Freedom from revascularisation and major adverse cardiovascular disease events, and attainment of the treatment goal between anatomical groups will be compared using Kaplan-Meier survival curves.
Ethisc and dissemination: This study has been exempted from formal medical ethical approval by the Medical Research Ethics Committees United 'MEC-U' (W17.071). Results are intended for publication in peer-reviewed journals and for presentation to stakeholders nationally and internationally.
Trial registration number: NTR7332; Pre-results.

Gepubliceerd: BMJ Open 2019 Feb 19;9(2):e025419
Impact factor: 2.376; Q2

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27. Implementation and outcome of minor and major minimally invasive liver surgery in the Netherlands

van der Poel MJ, Fichtinger RS, Bemelmans M, Bosscha K, Braat AE, de Boer MT, Dejong CHC, Doornebosch PG, Draaisma WA, Gerhards MF, Gobardhan PD, Gorgec B, Hagendoorn J, Kazemier G, Klaase J, Leclercq WKG, Liem MS, Lips DJ, Marsman HA, Mieog JSD, Molenaar QI, Nieuwenhuijs VB, Nota CL, Patijn GA, Rijken AM, Slooter GD, Stommel MWJ, Swijnenburg RJ, Tanis PJ, Te Riele WW, Terkivatan T, van den Tol PM, van den Boezem PB, van der Hoeven JA, Vermaas M, Abu Hilal M, van Dam RM, Besselink MG

Background: While most of the evidence on minimally invasive liver surgery (MILS) is derived from expert centers, nationwide outcomes remain underreported. This study aimed to evaluate the implementation and outcome of MILS on a nationwide scale.
Methods: Electronic patient files were reviewed in all Dutch liver surgery centers and all patients undergoing MILS between 2011 and 2016 were selected. Operative outcomes were stratified based on extent of the resection and annual MILS volume.
Results: Overall, 6951 liver resections were included, with a median annual volume of 50 resections per center. The overall use of MILS was 13% (n = 916), which varied from 3% to 36% (P < 0.001) between centers. The nationwide use of MILS increased from 6% in 2011 to 23% in 2016 (P < 0.001). Outcomes of minor MILS were comparable with international studies (conversion 0-13%, mortality <1%). In centers which performed >/=20 MILS annually, major MILS was associated with less conversions (14 (11%) versus 41 (30%), P < 0.001), shorter operating time (184 (117-239) versus 200 (139-308) minutes, P = 0.010), and less overall complications (37 (30%) versus 58 (42%), P = 0.040).
Conclusion: The nationwide use of MILS is increasing, although large variation remains between centers. Outcomes of major MILS are better in centers with higher volumes.

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Impact factor: 3.047; Q1

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28. Nationwide Outcome of Gastrectomy with En-Bloc Partial Pancreatectomy for Gastric Cancer

van der Werf LR, Eshuis WJ, Draaisma WA, van Etten B, Gisbertz SS, van der Harst E, Liem MSL, Lemmens VEPP, Wijnhoven BPL, Besselink MG, van Berge Henegouwen MI

Background: Radical gastrectomy is the cornerstone of the treatment of gastric cancer. For tumors invading the pancreas, en-bloc partial pancreatectomy may be needed for a radical resection. The aim of this study was to evaluate the outcome of gastrectomies with partial pancreatectomy for gastric cancer.
Methods: Patients who underwent gastrectomy with or without partial pancreatectomy for gastric or gastro-oesophageal junction cancer between 2011 and 2015 were selected from the Dutch Upper GI Cancer Audit (DUCA). Outcomes were resection margin (pR0) and Clavien-Dindo grade >/= III postoperative complications and survival. The association between partial pancreatectomy and postoperative complications was analyzed with multivariable logistic regression. Overall survival of patients with partial pancreatectomy was estimated using the Kaplan-Meier method.

Results: Of 1966 patients that underwent gastrectomy, 55 patients (2.8%) underwent en-bloc partial pancreatectomy. A pR0 resection was achieved in 45 of 55 patients (82% versus 85% in the group without additional resection, P = 0.82). Clavien-Dindo grade >/= III complications occurred in 21 of 55 patients (38% versus 17%, P < 0.001). Median overall survival [95% confidence interval] was 15 [6.8-23.2] months. For patients with and without perioperative systemic therapy, median survival was 20 [12.3-27.7] and 10 [5.7-14.3] months, and for patients with pR0 and pR1 resection, it was 20 [11.8-28.3] and 5 [2.4-7.6] months, respectively.
Conclusions: Gastrectomy with partial pancreatectomy is not only associated with a pR0 resection rate of 82% but also with increased postoperative morbidity. It should only be performed if a pR0 resection is feasible.

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Impact factor: 2.686; Q2

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29. Restrictive strategy versus usual care for cholecystectomy in patients with gallstones and abdominal pain (SECURE): a multicentre, randomised, parallel-arm, non-inferiority trial
van Dijk AH, Wennmacker SZ, de Reuver PR, Latenstein CSS, Buyne O, Donkervoort SC, Eijsbouts QAJ, Heisterkamp J, Hof KI', Janssen J, Nieuwenhuijs VB, Schaap HM, Steenvoorde P, Stockmann HBAC, Boerma D, Westert GP, Drenth JPH, Dijkgraaf MGW, Boermeester MA, van Laarhoven CJHM

Background: International guidelines advise laparoscopic cholecystectomy to treat symptomatic, uncomplicated gallstones. Usual care regarding cholecystectomy is associated with practice variation and persistent post-cholecystectomy pain in 10-41% of patients. We aimed to compare the non-inferiority of a restrictive strategy with stepwise selection with usual care to assess (in)efficient use of cholecystectomy.
Methods: We did a multicentre, randomised, parallel-arm, non-inferiority study in 24 academic and non-academic hospitals in the Netherlands. We enrolled patients aged 18-95 years with abdominal pain and ultrasound-proven gallstones or sludge. Patients were randomly assigned (1:1) to either usual care in which selection for cholecystectomy was left to the discretion of the surgeon, or a restrictive strategy with stepwise selection for cholecystectomy. For the restrictive strategy, cholecystectomy was advised for patients who fulfilled all five pre-specified criteria of the triage instrument: 1) severe pain attacks, 2) pain lasting 15-30 min or longer, 3) pain located in epigastrium or right upper quadrant, 4) pain radiating to the back, and 5) a positive pain response to simple analgesics. Randomisation was done with an online program, implemented into a web-based application using blocks of variable sizes, and stratified for centre (academic versus non-academic and a high vs low number of patients), sex, and body-mass index. Physicians and patients were masked for study-arm allocation until after completion of the triage instrument. The primary, non-inferiority, patient-reported endpoint was the proportion of patients who were pain-free at 12 months' follow-up, analysed by intention to treat and per protocol. A 5% non-inferiority margin was chosen, based on the estimated clinically relevant difference. Safety analyses were also done in the intention-to treat population. This trial is registered at the Netherlands National Trial Register, number NTR4022.
Findings: Between Feb 5, 2014, and April 25, 2017, we included 1067 patients for analysis: 537 assigned to usual care and 530 to the restrictive strategy. At 12 months'

follow-up 298 patients (56%; 95% CI, 52.0-60.4) were pain-free in the restrictive strategy group, compared with 321 patients (60%, 55.6-63.8) in usual care. Non-inferiority was not shown (difference 3.6%; one-sided 95% lower CI -8.6%; pnon-inferiority=0.316). According to a secondary endpoint analysis, the restrictive strategy resulted in significantly fewer cholecystectomies than usual care (358 [68%] of 529 vs 404 [75%] of 536; p=0.01). There were no between-group differences in trial-related gallstone complications (40 patients [8%] of 529 in usual care vs 38 [7%] of 536 in restrictive strategy; p=0.16) and surgical complications (74 [21%] of 358 vs 88 [22%] of 404, p=0.77), or in non-trial-related serious adverse events (27 [5%] of 529 vs 29 [5%] of 526).
Interpretation: Suboptimal pain reduction in patients with gallstones and abdominal pain was noted with both usual care and following a restrictive strategy for selection for cholecystectomy. However, the restrictive strategy was associated with fewer cholecystectomies. The findings should encourage physicians involved in the care of patients with gallstones to rethink cholecystectomy, and to be more careful in advising a surgical approach in patients with gallstones and abdominal symptoms.
Funding: The Netherlands Organization for Health Research and Development, and CZ healthcare insurance.

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Impact factor: 59.102; Q1

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30. Clinical management of chronic mesenteric ischemia
van Dijk LJ, van Noord D, de Vries AC, Kolkman JJ, Geelkerken RH, Verhagen HJ, Moelker A, Bruno MJ

This This Dutch Mesenteric Ischemia Study group consists of: Ron Balm, Academic Medical Center, Amsterdam Gert Jan de Borst, University Medical Center Utrecht, Utrecht Juliette T Blauw, Medisch Spectrum Twente, Enschede Marco J Bruno, Erasmus MC University Medical Center, Rotterdam Olaf J Bakker, St Antonius Hospital, Nieuwegein Louisa JD van Dijk, Erasmus MC University Medical Center, Rotterdam Hessel CJL Buscher, Gelre Hospitals, Apeldoorn Bram Fioole, Maasstad Hospital, Rotterdam Robert H Geelkerken, Medisch Spectrum Twente, Enschede Jaap F Hamming, Leiden University Medical Center, Leiden Jihan Harki, Erasmus MC University Medical Center, Rotterdam Daniel AF van den Heuvel, St Antonius Hospital, Nieuwegein Eline S van Hattum, University Medical Center Utrecht, Utrecht Jan Willem Hinnen, Jeroen Bosch Hospital, 's-Hertogenbosch Jeroen J Kolkman, Medisch Spectrum Twente, Enschede Maarten J van der Laan, University Medical Center Groningen, Groningen Kaatje Lenaerts, Maastricht University Medical Center, Maastricht Adriaan Moelker, Erasmus MC University Medical Center, Rotterdam Desiree van Noord, Franciscus Gasthuis & Vlietland, Rotterdam Maikel P Peppelenbosch, Erasmus MC University Medical Center, Rotterdam Andre S van Petersen, Bernhoven Hospital, Uden Pepijn Rijnja, Medisch Spectrum Twente, Enschede Peter J van der Schaar, St Antonius Hospital, Nieuwegein Luke G Terlouw, Erasmus MC University Medical Center, Rotterdam Hence JM Verhagen, Erasmus MC University Medical Center, Rotterdam Jean Paul PM de Vries, University Medical Center Groningen, Groningen Dammis Vroegindeweij, Maasstad Hospital, Rotterdam review provides an overview on the clinical management of chronic mesenteric ischemia (CMI). CMI is defined as insufficient blood supply to the gastrointestinal

tract, most often caused by atherosclerotic stenosis of one or more mesenteric arteries. Patients classically present with postprandial abdominal pain and weight loss. However, patients may present with, atypically, symptoms such as abdominal discomfort, nausea, vomiting, diarrhea or constipation. Early consideration and diagnosis of CMI is important to timely treat, to improve quality of life and to prevent acute-on-chronic mesenteric ischemia. The diagnosis of CMI is based on the triad of clinical symptoms, radiological evaluation of the mesenteric vasculature and if available, functional assessment of mucosal ischemia. Multidisciplinary consensus on the diagnosis of CMI is of paramount importance to adequately select patients for treatment. Patients with a consensus diagnosis of single-vessel or multi-vessel atherosclerotic CMI are preferably treated with endovascular revascularization.

Gepubliceerd: United European Gastroenterol J 2019 Mar;7(2):179-88
Impact factor: 3.453; Q2

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31. Validation of a score chart to predict the risk of chronic mesenteric ischemia and development of an updated score chart
van Dijk LJ, van Noord D, Geelkerken RH, Harki J, Berendsen SA, de Vries AC, Moelker A, Vergouwe Y, Verhagen HJ, Kolkman JJ, Bruno MJ

Background and objective: The objective of this article is to externally validate and update a recently published score chart for chronic mesenteric ischemia (CMI).
Methods: A multicenter prospective cohort analysis was conducted of 666 CMI-suspected patients referred to two Dutch specialized CMI centers. Multidisciplinary consultation resulted in expert-based consensus diagnosis after which CMI consensus patients were treated. A definitive diagnosis of CMI was established if successful treatment resulted in durable symptom relief. The absolute CMI risk was calculated and discriminative ability of the original chart was assessed by the c-statistic in the validation cohort. Thereafter the original score chart was updated based on the performance in the combined original and validation cohort with inclusion of celiac artery (CA) stenosis cause.
Results: In 8% of low-risk patients, 39% of intermediate-risk patients and 94% of high-risk patients of the validation cohort, CMI was diagnosed. Discriminative ability of the original model was acceptable (c-statistic 0.79). The total score of the updated chart ranged from 0 to 28 points (low risk 19% absolute CMI risk, intermediate risk 45%, and high risk 92%). The discriminative ability of the updated chart was slightly better (c-statistic 0.80).
Conclusion: The CMI prediction model performs and discriminates well in the validation cohort. The updated score chart has excellent discriminative ability and is useful in clinical decision making.

Gepubliceerd: United European Gastroenterol J 2019 Nov;7(9):1261-70
Impact factor: 3.453; Q2

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32. Covered stents versus Bare-metal stents in chronic atherosclerotic Gastrointestinal Ischemia (CoBaGI): study protocol for a randomized controlled trial

van Dijk LJD, Harki J, van ND, Verhagen HJM, Kolkman JJ, Geelkerken RH, Bruno MJ, Moelker A

Background: Chronic mesenteric ischemia (CMI) is the result of insufficient blood supply to the gastrointestinal tract and is caused by atherosclerotic stenosis of one or more mesenteric arteries in > 90% of cases. Revascularization therapy is indicated in patients with a diagnosis of atherosclerotic CMI to relieve symptoms and to prevent acute-on-chronic mesenteric ischemia, which is associated with high morbidity and mortality. Endovascular therapy has rapidly evolved and has replaced surgery as the first choice of treatment in CMI. Bare-metal stents (BMS) are standard care currently, although retrospective studies suggested significantly higher patency rates for covered stents (CS). The Covered stents versus Bare-metal stents in chronic atherosclerotic Gastrointestinal Ischemia (CoBaGI) trial is designed to prospectively assess the patency of CS versus BMS in patients with atherosclerotic CMI.
Methods/Design: The CoBaGI trial is a randomized controlled, parallel-group, patient- and investigator-blinded, superiority, multicenter trial conducted in six centers of the Dutch Mesenteric Ischemia Study group (DMIS). Eighty-four patients with a consensus diagnosis of atherosclerotic CMI are 1:1 randomized to either a balloon-expandable BMS (Palmaz Blue with rapid-exchange delivery system, Cordis Corporation, Bridgewater, NJ, USA) or a balloon-expandable CS (Advanta V12 over-the-wire, Atrium Maquet Getinge Group, Hudson, NH, USA). The primary endpoint is the primary stent-patency rate at 24 months assessed with CT angiography. Secondary endpoints are primary stent patency at 6 and 12 months and secondary patency rates, freedom from restenosis, freedom from symptom recurrence, freedom from re-intervention, quality of life according the EQ-5D-5 L and SF-36 and cost-effectiveness at 6, 12 and 24 months.
Discussion: The CoBaGI trial is designed to assess the patency rates of CS versus BMS in patients treated for CMI caused by atherosclerotic mesenteric stenosis. Furthermore, the CoBaGI trial should provide insights in the quality of life of these patients before and after stenting and its cost-effectiveness. The CoBaGI trial is the first randomized controlled trial performed in CMI caused by atherosclerotic mesenteric artery stenosis.
Trial Registration: ClinicalTrials.gov, ID: NCT02428582 . Registered on 29 April 2015.

Gepubliceerd: Trials 2019 Aug 20;20(1):519
Impact factor: 1.975; Q3

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33. Laparoscopic pancreatoduodenectomy with open or laparoscopic reconstruction during the learning curve: a multicenter propensity score matched study

van Hilst J, de Rooij T, van den Boezem PB, Bosscha K, Busch OR, van Duijvendijk P, Festen S, Gerhards MF, de Hingh IH, Karsten TM, Kazemier G, Lips DJ, Luyer MD, Nieuwenhuijs VB, Patijn GA, Stommel MW, Zonderhuis BM, Daams F, Besselink MG

Background: Laparoscopic pancreatoduodenectomy with open reconstruction (LPD-OR) has been suggested to lower the rate of postoperative pancreatic fistula reported

after laparoscopic pancreatoduodenectomy with laparoscopic reconstruction (LPD). Propensity score matched studies are, lacking.
Methods: This is a multicenter prospective cohort study including patients from 7 Dutch centers between 2014-2018. Patients undergoing LPD-OR were matched LPD patients in a 1:1 ratio based on propensity scores. Main outcomes were postoperative pancreatic fistulas (POPF) grade B/C and Clavien-Dindo grade >/=3 complications.
Results: A total of 172 patients were included, involving the first procedure for all centers. All 56 patients after LPD-OR could be matched to a patient undergoing LPD. With LPD-OR, the unplanned conversion rate was 21% vs. 9% with LPD (P < 0.001). Median blood loss (300 vs. 400 mL, P = 0.85), operative time (401 vs. 378 min, P = 0.62) and hospital stay (10 vs. 12 days, P = 0.31) were comparable for LPD-OR vs. LPD, as were Clavien-Dindo grade >/=3 complications (38% vs. 52%, P = 0.13), POPF grade B/C (23% vs. 21%, P = 0.82), and 90-day mortality (4% vs. 4%, P > 0.99).
Conclusion: In this propensity matched cohort performed early in the learning curve, no benefit was found for LPD-OR, as compared to LPD.

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Impact factor: 3.047; Q1

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34. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial
van Hilst J, de Rooij T, Bosscha K, Brinkman DJ, van Dieren S, Dijkgraaf MG, Gerhards MF, de Hingh IH, Karsten TM, Lips DJ, Luyer MD, Busch OR, Festen S, Besselink MG

Background: Laparoscopic pancreatoduodenectomy may improve postoperative recovery compared with open pancreatoduodenectomy. However, there are concerns that the extensive learning curve of this complex procedure could increase the risk of complications. We aimed to assess whether laparoscopic pancreatoduodenectomy could reduce time to functional recovery compared with open pancreatoduodenectomy.
Methods: This multicentre, patient-blinded, parallel-group, randomised controlled phase 2/3 trial was performed in four centres in the Netherlands that each do 20 or more pancreatoduodenectomies annually; surgeons had to have completed a dedicated training programme for laparoscopic pancreatoduodenectomy and have done 20 or more laparoscopic pancreatoduodenectomies before trial participation. Patients with a benign, premalignant, or malignant indication for pancreatoduodenectomy, without signs of vascular involvement, were randomly assigned (1:1) to undergo either laparoscopic or open pancreatoduodenectomy using a central web-based system. Randomisation was stratified for annual case volume and preoperative estimated risk of pancreatic fistula. Patients were blinded to treatment allocation. Analysis was done according to the intention-to-treat principle. The main objective of the phase 2 part of the trial was to assess the safety of laparoscopic pancreatoduodenectomy (complications and mortality), and the primary outcome of phase 3 was time to functional recovery in days, defined as all of the following: adequate pain control with only oral analgesia; independent mobility; ability to maintain more than 50% of the daily required caloric intake; no need for

intravenous fluid administration; and no signs of infection (temperature <38.5 degrees C). This trial is registered with Trialregister.nl, number NTR5689.
Findings: Between May 13 and Dec 20, 2016, 42 patients were randomised in the phase 2 part of the trial. Two patients did not receive surgery and were excluded from analyses in accordance with the study protocol. Three (15%) of 20 patients died within 90 days after laparoscopic pancreatoduodenectomy, compared with none of 20 patients after open pancreatoduodenectomy. Based on safety data from the phase 2 part of the trial, the data and safety monitoring board and protocol committee agreed to proceed with phase 3. Between Jan 31 and Nov 14, 2017, 63 additional patients were randomised in phase 3 of the trial. Four patients did not receive surgery and were excluded from analyses in accordance with the study protocol. After randomisation of 105 patients (combining patients from both phase 2 and phase 3), of whom 99 underwent surgery, the trial was prematurely terminated by the data and safety monitoring board because of a difference in 90-day complication-related mortality (five [10%] of 50 patients in the laparoscopic pancreatoduodenectomy group vs one [2%] of 49 in the open pancreatoduodenectomy group; risk ratio [RR] 4.90 [95% CI 0.59-40.44]; p=0.20). Median time to functional recovery was 10 days (95% CI 5-15) after laparoscopic pancreatoduodenectomy versus 8 days (95% CI 7-9) after open pancreatoduodenectomy (log-rank p=0.80). Clavien-Dindo grade III or higher complications (25 [50%] of 50 patients after laparoscopic pancreatoduodenectomy vs 19 [39%] of 49 after open pancreatoduodenectomy; RR 1.29 [95% CI 0.82-2.02]; p=0.26) and grade B/C postoperative pancreatic fistulas (14 [28%] vs 12 [24%]; RR 1.14 [95% CI 0.59-2.22]; p=0.69) were comparable between groups.
Interpretation: Although not statistically significant, laparoscopic pancreatoduodenectomy was associated with more complication-related deaths than was open pancreatoduodenectomy, and there was no difference between groups in time to functional recovery. These safety concerns were unexpected and worrisome, especially in the setting of trained surgeons working in centres performing 20 or more pancreatoduodenectomies annually. Experience, learning curve, and annual volume might have influenced the outcomes; future research should focus on these issues.
Funding: Grant for investigator-initiated studies by Johnson & Johnson Medical Limited.

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Impact factor: 0; nvt

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35. Radiation exposure in an endovascular aortic aneurysm repair program after introduction of a hybrid operating theater
Wermelink B, Willigendael EM, Smit C, Beuk RJ, Brusse-Keizer M, Meerwaldt R, Geelkerken RH

Background: A hybrid operating theater (HOT) enables optimal image quality, improved ergonomics, and excellent sterility for complex endovascular and hybrid procedures. We hypothesize that the commissioning of a new HOT involves a learning curve. It is unclear how steep the learning curve of these advanced HOTs is. The main purpose of this research was to evaluate radiation exposure parameters in a new HOT for a team of vascular surgeons experienced with infrarenal endovascular aneurysm repair (EVAR) procedures in a conventional operating room with a mobile

C-arm. In addition, a comparison of the dose-area product (DAP) achieved in this study and in the literature was made.
Methods: Before commissioning of the HOT, four vascular surgeons completed a comprehensive HOT training program. From the commissioning of the HOT, clinical and procedural data for all consecutive acute and elective patients treated with EVAR were retrospectively collected for a period of 18 months (January 2016-June 2017). A literature review was conducted of the dose-area product in EVAR procedures performed with a dedicated fixed system or mobile C-arm to analyze how this study performed compared with the literature.
Results: In the 18-month study period, 77 patients were treated with EVAR (59 electively and 18 acutely), from whom the data were obtained. There was no significant change in radiation exposure parameters over time. From the commissioning of the HOT, EVAR procedures were performed with radiation exposure parameters similar to those of studies found in experienced vascular centers using fixed systems.
Conclusions: Concerning radiation exposure parameters, the commissioning of a new HOT was not accompanied by a learning curve. Radiation exposure parameters achieved in this study were similar to those of studies from experienced and dedicated vascular centers.

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Impact factor: 3.243; Q1

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36. Added value of 3D-vision during laparoscopic biotissue pancreatico- and hepaticojejunostomy (LAELAPS 3D2D): an international randomized cross-over trial

Zwart MJW, Fuente I, Hilst J, de Rooij T, van Dieren S, van Rijssen LB, Schijven MP, Busch ORC, Luyer MD, Lips DJ, Festen S, Abu Hilal M, Besselink MG

Background: It is currently unclear what the added value is of 3D-laparoscopy during pancreatic and biliary surgery. 3D-laparoscopy could improve procedure time and/or surgical performance, for instance in demanding anastomoses such as pancreatico- and hepaticojejunostomy. The impact of 3D-laparoscopy could be negligible in more experienced surgeons.
Methods: We conducted a randomized controlled cross-over trial including 20 expert laparoscopic surgeons and 20 surgical residents from 9 countries (Argentina, Estonia, Israel, Italy, the Netherlands, South Africa, Spain, UK, USA). All participants performed a pancreaticojejunostomy (PJ) and a hepaticojejunostomy (HJ) using 3D- and 2D-laparoscopy on biotissue organ models according to the Pittsburgh method. Primary endpoint was the time required to complete both anastomoses. Secondary endpoint was the objective structured assessment of technical skill (OSATS; range 12-60) rating. Observers were blinded for 3D/2D and expertise.
Results: A total of 40 participants completed 144 PJs and HJs. 3D-laparoscopy reduced the operative time with 15.5 min (95%CI 10.2-24.5 min), from 81.0 to 64.4 min, p = 0.001. This reduction was observed for both experts and residents (13.0 vs 22.2 min, intergroup significance p = 0.354). The OSATS improved with 5.1 points, SD +/- 6.3, with 3D-laparoscopy, p = 0.001. This improvement was observed for both experts and residents (4.6 vs 5.6 points, p = 0.519). Of all participants, 37/39 participants stated to prefer 3D laparoscopy whereas 14/39 reported side effects.

Minor side effects were reported by 10/39 participants whereas 2/39 participants reported severe side effects (both severe eye strain).
Conclusion: 3D-laparoscopy, as compared to 2D-laparoscopy, reduced the operative time and improved surgical performance for PJ and HJ anastomoses in both experts and residents with mostly minor side effects.

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Impact factor: 3.047; Q1

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37. Postponed or immediate drainage of infected necrotizing pancreatitis (POINTER trial): study protocol for a randomized controlled trial
van Grinsven J, van Dijk SM, Dijkgraaf MG, Boermeester MA, Bollen TL, Bruno MJ, vanBrunschot S., Dejong CH, van Eijck CH, van Lienden KP, Boerma D, van Duijvendijk P, Hadithi M, Haveman JW, van der Hulst RW, Jansen JM, Lips DJ, Manusama ER, Molenaar IQ, van der Peet DL, Poen AC, Quispel R, Schaapherder AF, Schoon EJ, Schwartz MP, Seerden TC, Spanier BWM, Straathof JW, Venneman NG, van de Vrie W, Witteman BJ, van Goor H, Fockens P, van Santvoort HC, Besselink MG

Background: Infected necrosis complicates 10% of all acute pancreatitis episodes and is associated with 15-20% mortality. The current standard treatment for infected necrotizing pancreatitis is the step-up approach (catheter drainage, followed, if necessary, by minimally invasive necrosectomy). Catheter drainage is preferably postponed until the stage of walled-off necrosis, which usually takes 4 weeks. This delay stems from the time when open necrosectomy was the standard. It is unclear whether such delay is needed for catheter drainage or whether earlier intervention could actually be beneficial in the current step-up approach. The POINTER trial investigates if immediate catheter drainage in patients with infected necrotizing pancreatitis is superior to the current practice of postponed intervention.
Methods: POINTER is a randomized controlled multicenter superiority trial. All patients with necrotizing pancreatitis are screened for eligibility. In total, 104 adult patients with (suspected) infected necrotizing pancreatitis will be randomized to immediate (within 24 h) catheter drainage or current standard care involving postponed catheter drainage. Necrosectomy, if necessary, is preferably postponed until the stage of walled-off necrosis, in both treatment arms. The primary outcome is the Comprehensive Complication Index (CCI), which covers all complications between randomization and 6-month follow up. Secondary outcomes include mortality, complications, number of (repeat) interventions, hospital and intensive care unit (ICU) lengths of stay, quality-adjusted life years (QALYs) and direct and indirect costs. Standard follow-up is at 3 and 6 months after randomization.
Discussion: The POINTER trial investigates if immediate catheter drainage in infected necrotizing pancreatitis reduces the composite endpoint of complications, as compared with the current standard treatment strategy involving delay of intervention until the stage of walled-off necrosis.
Trial Registration: ISRCTN, 33682933 . Registered on 6 August 2015. Retrospectively registered.

Gepubliceerd: Trials 2019 Apr 25;20(1):239
Impact factor: 1.975; Q3

38. Toward Optimizing Risk Adjustment in the Dutch Surgical Aneurysm Audit
Lijftogt N, Vahl A, van der Willik EM, Leijdekkers VJ, Wouters MWJM, Hamming JF, Dutch Society of Vascular Surgery, the Steering Committee of the Dutch Surgical Aneurysm Audit and the Dutch Institute for Clinical Auditing, includes Beuk RJ, Geelkerken RH, Meerwaldt R, Willigendael EM

Background: To compare hospital outcomes of aortic aneurysm surgery, casemix correction for preoperative variables is essential. Most of these variables can be deduced from mortality risk prediction models. Our aim was to identify the optimal set of preoperative variables associated with mortality to establish a relevant and efficient casemix model.
Methods: All patients prospectively registered between 2013 and 2016 in the Dutch Surgical Aneurysm Audit (DSAA) were included for the analysis. After multiple imputation for missing variables, predictors for mortality following univariable logistic regression were analyzed in a manual backward multivariable logistic regression model and compared with three standard mortality risk prediction models: Glasgow Aneurysm Score (GAS, mainly clinical parameters), Vascular Biochemical and Haematological Outcome Model (VBHOM, mainly laboratory parameters), and Dutch Aneurysm Score (DAS, both clinical and laboratory parameters). Discrimination and calibration were tested and considered good with a C-statistic > 0.8 and Hosmer-Lemeshow (H-L) P > 0.05.
Results: There were 12,401 patients: 9,537 (76.9%) elective patients (EAAA), 913 (7.4%) acute symptomatic patients (SAAA), and 1,951 (15.7%) patients with acute rupture (RAAA). Overall postoperative mortality was 6.5%; 1.8% after EAAA surgery, 6.6% after SAAA, and 29.6% after RAAA surgery. The optimal set of independent variables associated with mortality was a mix of clinical and laboratory parameters: gender, age, pulmonary comorbidity, operative setting, creatinine, aneurysm size, hemoglobin, Glasgow coma scale, electrocardiography, and systolic blood pressure (C-statistic 0.871). External validation overall of VBHOM, DAS, and GAS revealed C-statistics of 0.836, 0.782, and 0.761, with an H-L of 0.028, 0.00, and 0.128, respectively.
Conclusions: The optimal set of variables for casemix correction in the DSAA comprises both clinical and laboratory parameters, which can be collected easily from electronic patient files and will lead to an efficient casemix model.

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Impact factor: 1.179; Q3

39. Costs and quality of life in a randomized trial comparing minimally invasive and open distal pancreatectomy (LEOPARD trial)
van Hilst J, Strating EA, de Rooij T, Daams F, Festen S, Groot Koerkamp B, Klaase JM, Luyer M, Dijkgraaf MG, Besselink MG, Dutch Pancreatic Cancer Group and LEOPARD trial collaborators, includes van Duyn EB, Steenvoorde P

Background: Minimally invasive distal pancreatectomy decreases time to functional recovery compared with open distal pancreatectomy, but the cost-effectiveness and impact on disease-specific quality of life have yet to be established.

Methods: The LEOPARD trial randomized patients to minimally invasive (robot-assisted or laparoscopic) or open distal pancreatectomy in 14 Dutch centres between April 2015 and March 2017. Use of hospital healthcare resources, complications and disease-specific quality of life were recorded up to 1 year after surgery. Unit costs of hospital healthcare resources were determined, and cost-effectiveness and cost-utility analyses were performed. Primary outcomes were the costs per day earlier functional recovery and per quality-adjusted life-year.
Results: All 104 patients who had a distal pancreatectomy (48 minimally invasive and 56 open) in the trial were included in this study. Patients who underwent a robot-assisted procedure were excluded from the cost analysis. Total medical costs were comparable after laparoscopic and open distal pancreatectomy (mean difference euro-427 (95 per cent bias-corrected and accelerated confidence interval euro-4700 to 3613; P = 0.839). Laparoscopic distal pancreatectomy was shown to have a probability of at least 0.566 of being more cost-effective than the open approach at a willingness-to-pay threshold of euro0 per day of earlier recovery, and a probability of 0.676 per additional quality-adjusted life-year at a willingness-to-pay threshold of euro80 000. There were no significant differences in cosmetic satisfaction scores (median 9 (i.q.r. 5.75-10) versus 7 (4-8.75); P = 0.056) and disease-specific quality of life after minimally invasive (laparoscopic and robot-assisted procedures) versus open distal pancreatectomy.
Conclusion: Laparoscopic distal pancreatectomy was at least as cost-effective as open distal pancreatectomy in terms of time to functional recovery and quality-adjusted life-years. Cosmesis and quality of life were similar in the two groups 1 year after surgery.

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Impact factor: 5.572; Q1

Totale impact factor: 216.047
Gemiddelde impact factor: 5.540

Aantal artikelen 1e, 2e of laatste auteur: 13
Totale impact factor: 40.959
Gemiddelde impact factor: 3.151

Intensive Care

1. Additional filtering of blood from a cell salvage device is not likely to show important additional benefits in outcome in cardiac surgery
de Vries AJ, Vermeijden WJ, van Pelt LJ, van den Heuvel ER, van Oeveren W

Background: Several authors and manufacturers of cell salvage devices recommend additional filtering of processed blood before transfusion. There is no evidence to support this practice. Therefore, we compared the clinical outcome and biochemical effects of cell salvage with or without additional filtering.
Study design and methods: The patients, scheduled for coronary artery bypass grafting, valve replacement, or combined procedures were part of our randomized multicenter factorial study of cell salvage and filter use on transfusion requirements (ISRCTN 58333401). They were randomized to intraoperative cell salvage or cell salvage plus additional WBC depletion filter. We compared the occurrence of major adverse events (combined death/stroke/myocardial infarction) as primary outcome and minor adverse events (renal function disturbances, infections, delirium), ventilation time, and length of stay in the intensive care unit and hospital. We also measured biochemical markers of organ injury and inflammation.
Results: One hundred eighty-nine patients had cell salvage, and 175 patients had cell salvage plus filter and completed the study. Demographic data, surgical procedures, and amount of salvaged blood were not different between the groups. There was no difference in the primary outcome with a risk of 6.3% (95% confidence interval [CI], 3.34-11.25) in the cell salvage plus filter group versus 5.8% (95% CI, 3.09-10.45) in the cell salvage group, a relative risk of 1.08 (95% CI, 0.48- 2.43]. There were no differences in minor adverse events and biochemical markers between the groups.
Conclusion: The routine use of an additional filter for transfusion of salvaged blood is unlikely to show important additional benefits.

Gepubliceerd: Transfusion 2019 Mar;59(3):989-94
Impact factor: 3.111; Q2

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2. A multicenter, randomized, double-blind study of ulimorelin and metoclopramide in the treatment of critically ill patients with enteral feeding intolerance: PROMOTE trial
Heyland DK, van Zanten ARH, Grau-Carmona T, Evans D, Beishuizen A, Schouten J, Hoiting O, Bordeje ML, Krell K, Klein DJ, Gonzalez J, Perez A, Brown R, James J, Harris MS

Purpose: Enteral feeding intolerance (EFI) is a frequent problem in the intensive care unit (ICU), but current prokinetic agents have uncertain efficacy and safety profiles. The current study compared the efficacy and safety of ulimorelin, a ghrelin agonist, with metoclopramide in the treatment of EFI.
Methods: One hundred twenty ICU patients were randomized 1:1 to ulimorelin or metoclopramide for 5 days. EFI was diagnosed by a gastric residual volume (GRV) >/= 500 ml. A volume-based feeding protocol was employed, and enteral formulas were standardized. The primary end point was the percentage daily protein

prescription (%DPP) received by patients over 5 days of treatment. Secondary end points included feeding success, defined as 80% DPP; gastric emptying, assessed by paracetamol absorption; incidences of recurrent intolerance (GRV >/= 500 ml); vomiting or regurgitation; aspiration, defined by positive tracheal aspirates for pepsin; and pulmonary infection.
Results: One hundred twenty patients were randomized and received the study drug (ulimorelin 62, metoclopramide 58). Mean APACHE II and SOFA scores were 21.6 and 8.6, and 63.3% of patients had medical reasons for ICU admission. Ulimorelin and metoclopramide resulted in comparable %DPPs over 5 days of treatment (median [Q1, Q3]: 82.9% [38.4%, 100.2%] and 82.3% [65.6%, 100.2%], respectively, p = 0.49). Five-day rates of feeding success were 67.7% and 70.6% when terminations unrelated to feeding were excluded, and there were no differences in any secondary outcomes or adverse events between the two groups.
Conclusions: Both prokinetic agents achieved similar rates of feeding success, and no safety differences between the two treatment groups were observed.

Gepubliceerd: Intensive Care Med 2019 May;45(5):647-56
Impact factor: 18.967; Q1

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3. Coronary Angiography after Cardiac Arrest without ST-Segment Elevation
Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak R, Vlachojannis GJ, Eikemans BJW, van der Harst P, van der Horst ICC, Voskuil M, van der Heijden JJ, Beishuizen A, Stoel M, Camaro C, van der Hoeven H, Henriques JP, Vlaar APJ, Vink MA, van den Bogaard B, Heestermans TACM, de RW, Delnoij TSR, Crijns HJGM, Jessurun GAJ, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, van de Ven PM, Oudemans-van Straaten HM, van Royen N

Background: Ischemic heart disease is a major cause of out-of-hospital cardiac arrest. The role of immediate coronary angiography and percutaneous coronary intervention (PCI) in the treatment of patients who have been successfully resuscitated after cardiac arrest in the absence of ST-segment elevation myocardial infarction (STEMI) remains uncertain.
Methods: In this multicenter trial, we randomly assigned 552 patients who had cardiac arrest without signs of STEMI to undergo immediate coronary angiography or coronary angiography that was delayed until after neurologic recovery. All patients underwent PCI if indicated. The primary end point was survival at 90 days. Secondary end points included survival at 90 days with good cerebral performance or mild or moderate disability, myocardial injury, duration of catecholamine support, markers of shock, recurrence of ventricular tachycardia, duration of mechanical ventilation, major bleeding, occurrence of acute kidney injury, need for renal-replacement therapy, time to target temperature, and neurologic status at discharge from the intensive care unit.
Results: At 90 days, 176 of 273 patients (64.5%) in the immediate angiography group and 178 of 265 patients (67.2%) in the delayed angiography group were alive (odds ratio, 0.89; 95% confidence interval [CI], 0.62 to 1.27; P = 0.51). The median time to target temperature was 5.4 hours in the immediate angiography group and 4.7 hours in the delayed angiography group (ratio of geometric means, 1.19; 95% CI, 1.04 to 1.36). No significant differences between the groups were found in the remaining secondary end points.

Conclusions: Among patients who had been successfully resuscitated after out-of-hospital cardiac arrest and had no signs of STEMI, a strategy of immediate angiography was not found to be better than a strategy of delayed angiography with respect to overall survival at 90 days. (Funded by the Netherlands Heart Institute and others; COACT Netherlands Trial Register number, NTR4973.).

Gepubliceerd: N Engl J Med 2019 Apr 11;380(15):1397-407
Impact factor: 70.670; Q1

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4. Prophylactic Haloperidol Effects on Long-term Quality of Life in Critically Ill Patients at High Risk for Delirium: Results of the REDUCE Study
Rood PJT, Zegers M, Slooter AJC, Beishuizen A, Simons KS, van der Voort PHJ, van der Woude MCE, Spronk PE, van der Hoeven JG, Pickkers P, van den Boogaard M

Background: Delirium incidence in intensive care unit patients is high and associated with impaired long-term outcomes. The use of prophylactic haloperidol did not improve short-term outcome among critically ill adults at high risk of delirium. This study evaluated the effects of prophylactic haloperidol use on long-term quality of life in this group of patients and explored which factors are associated with change in quality of life.
Methods: A preplanned secondary analysis of long-term outcomes of the pRophylactic haloperidol usE for DeliriUm in iCu patients at high risk for dElirium (REDUCE) study was conducted. In this multicenter randomized clinical trial, nondelirious intensive care unit patients were assigned to prophylactic haloperidol (1 or 2 mg) or placebo (0.9% sodium chloride). In all groups, patients finally received study medication for median duration of 3 days [interquartile range, 2 to 6] until onset of delirium or until intensive care unit discharge. Long-term outcomes were assessed using the Short Form-12 questionnaire at intensive care unit admission (baseline) and after 1 and 6 months. Quality of life was summarized in the physical component summary and mental component summary scores. Differences between the haloperidol and placebo group and factors associated with changes in quality of life were analyzed.
Results: Of 1,789 study patients, 1,245 intensive care unit patients were approached, of which 887 (71%) responded. Long-term quality of life did not differ between the haloperidol and placebo group (physical component summary mean score of 39 +/- 11 and 39 +/- 11, respectively, and P = 0.350; and mental component summary score of 50 +/- 10 and 51 +/- 10, respectively, and P = 0.678). Age, medical and trauma admission, quality of life score at baseline, risk for delirium (PRE-DELIRIC) score, and the number of sedation-induced coma days were significantly associated with a decline in long-term quality of life.
Conclusions: Prophylactic haloperidol use does not affect long-term quality of life in critically ill patients at high risk for delirium. Several factors, including the modifiable factor number of sedation-induced coma days, are associated with decline in long-term outcomes.

Gepubliceerd: Anesthesiology 2019 Aug;131(2):328-35
Impact factor: 6.424; Q1

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5. Early electroencephalography for outcome prediction of postanoxic coma: A prospective cohort study
Ruijter BJ, Tjepkema-Cloostermans MC, Tromp SC, van den Bergh WM, Foudraine NA, Kornips FHM, Drost G, Scholten E, Bosch FH, Beishuizen A, van Putten MJAM, Hofmeijer J

Objective: To provide evidence that early electroencephalography (EEG) allows for reliable prediction of poor or good outcome after cardiac arrest.
Methods: In a 5-center prospective cohort study, we included consecutive, comatose survivors of cardiac arrest. Continuous EEG recordings were started as soon as possible and continued up to 5 days. Five-minute EEG epochs were assessed by 2 reviewers, independently, at 8 predefined time points from 6 hours to 5 days after cardiac arrest, blinded for patients' actual condition, treatment, and outcome. EEG patterns were categorized as generalized suppression (<10 muV), synchronous patterns with >/=50% suppression, continuous, or other. Outcome at 6 months was categorized as good (Cerebral Performance Category [CPC] = 1-2) or poor (CPC = 3-5).
Results: We included 850 patients, of whom 46% had a good outcome. Generalized suppression and synchronous patterns with >/=50% suppression predicted poor outcome without false positives at >/=6 hours after cardiac arrest. Their summed sensitivity was 0.47 (95% confidence interval [CI] = 0.42-0.51) at 12 hours and 0.30 (95% CI = 0.26-0.33) at 24 hours after cardiac arrest, with specificity of 1.00 (95% CI = 0.99-1.00) at both time points. At 36 hours or later, sensitivity for poor outcome was </=0.22. Continuous EEG patterns at 12 hours predicted good outcome, with sensitivity of 0.50 (95% CI = 0.46-0.55) and specificity of 0.91 (95% CI = 0.88-0.93); at 24 hours or later, specificity for the prediction of good outcome was <0.90.
Interpretation: EEG allows for reliable prediction of poor outcome after cardiac arrest, with maximum sensitivity in the first 24 hours. Continuous EEG patterns at 12 hours after cardiac arrest are associated with good recovery.

Gepubliceerd: Ann Neurol 2019 Aug;86(2):203-14
Impact factor: 9.496; Q1

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6. Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use
Schuetz P, Beishuizen A, Broyles M, Ferrer R, Gavazzi G, Gluck EH, Gonzalez Del Castillo J, Jensen JU, Kanizsai PL, Kwa ALH, Krueger S, Luyt CE, Oppert M, Plebani M, Shlyapnikov SA, Toccafondi G, Townsend J, Welte T, Saeed K

Background: Procalcitonin (PCT)-guided antibiotic stewardship (ABS) has been shown to reduce antibiotics (ABxs), with lower side-effects and an improvement in clinical outcomes. The aim of this experts workshop was to derive a PCT algorithm ABS for easier implementation into clinical routine across different clinical settings.
Methods: Clinical evidence and practical experience with PCT-guided ABS was analyzed and discussed, with a focus on optimal PCT use in the clinical context and increased adherence to PCT protocols. Using a Delphi process, the experts group reached consensus on different PCT algorithms based on clinical severity of the patient and probability of bacterial infection.

Results: The group agreed that there is strong evidence that PCT-guided ABS supports individual decisions on initiation and duration of ABx treatment in patients with acute respiratory infections and sepsis from any source, thereby reducing overall ABx exposure and associated side effects, and improving clinical outcomes. To simplify practical application, the expert group refined the established PCT algorithms by incorporating severity of illness and probability of bacterial infection and reducing the fixed cut-offs to only one for mild to moderate and one for severe disease (0.25 mug/L and 0.5 mug/L, respectively). Further, guidance on interpretation of PCT results to initiate, withhold or discontinue ABx treatment was included.
Conclusions: A combination of clinical patient assessment with PCT levels in well-defined ABS algorithms, in context with continuous education and regular feedback to all ABS stakeholders, has the potential to improve the diagnostic and therapeutic management of patients suspected of bacterial infection, thereby improving ABS effectiveness.

Gepubliceerd: Clin Chem Lab Med 2019 Aug 27;57(9):1308-18
Impact factor: 3.638; Q1

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7. Outcome Prediction in Postanoxic Coma With Deep Learning
Tjepkema-Cloostermans MC, da Silva Lourenco C, Ruijter BJ, Tromp SC, Drost G, Kornips FHM, Beishuizen A, Bosch FH, Hofmeijer J, van Putten MJAM

Objectives: Visual assessment of the electroencephalogram by experienced clinical neurophysiologists allows reliable outcome prediction of approximately half of all comatose patients after cardiac arrest. Deep neural networks hold promise to achieve similar or even better performance, being more objective and consistent.
Design: Prospective cohort study.
Setting: Medical ICU of five teaching hospitals in the Netherlands.
Patients: Eight-hundred ninety-five consecutive comatose patients after cardiac arrest.
Interventions: None.
Measurements and main results: Continuous electroencephalogram was recorded during the first 3 days after cardiac arrest. Functional outcome at 6 months was classified as good (Cerebral Performance Category 1-2) or poor (Cerebral Performance Category 3-5). We trained a convolutional neural network, with a VGG architecture (introduced by the Oxford Visual Geometry Group), to predict neurologic outcome at 12 and 24 hours after cardiac arrest using electroencephalogram epochs and outcome labels as inputs. Output of the network was the probability of good outcome. Data from two hospitals were used for training and internal validation (n = 661). Eighty percent of these data was used for training and cross-validation, the remaining 20% for independent internal validation. Data from the other three hospitals were used for external validation (n = 234). Prediction of poor outcome was most accurate at 12 hours, with a sensitivity in the external validation set of 58% (95% CI, 51-65%) at false positive rate of 0% (CI, 0-7%). Good outcome could be predicted at 12 hours with a sensitivity of 48% (CI, 45-51%) at a false positive rate of 5% (CI, 0-15%) in the external validation set.
Conclusions: Deep learning of electroencephalogram signals outperforms any previously reported outcome predictor of coma after cardiac arrest, including visual electroencephalogram assessment by trained electroencephalogram experts. Our

approach offers the potential for objective and real time, bedside insight in the neurologic prognosis of comatose patients after cardiac arrest.

Gepubliceerd: Crit Care Med 2019 Oct;47(10):1424-32
Impact factor: 6.971; Q1

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8. Why would procalcitonin perform better in patients with a SOFA-score less than 8?
van Oers JAH, Nijsten MW, de Jong E, Beishuizen A, de Lange DW

Gepubliceerd: Int J Infect Dis 2019 Oct 1;89:185-6
Impact factor: 3.538; Q2

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9. Postmortem histopathology of electroencephalography and evoked potentials in postanoxic coma
van Putten MJAM, Jansen C, Tjepkema-Cloostermans MC, Beernink TMJ, Koot R, Bosch F, Beishuizen A, Hofmeijer J

Early EEG patterns and SSEP responses are associated with neurological recovery of comatose patients with postanoxic encephalopathy after cardiac arrest. However, the nature and distribution of brain damage underlying the characteristic EEG and SSEP patterns are unknown. We relate EEG and SSEP findings with results from histological analyses of the brains of eleven non-survivors. With restoration towards continuous rhythms within 24h after cardiac arrest, no signs of structural neuronal damage were observed. Absent SSEP responses were always accompanied by thalamic damage. Pathological burst suppression patterns were associated with a variable degree of neuronal damage to cortex, cerebellum and hippocampus. In patients with additional thalamic involvement, burst-suppression with identical bursts was observed, a characteristic EEG pattern presumably reflecting residual activity from a relatively isolated and severely compromised cortex.

Gepubliceerd: Resuscitation 2019 Jan;134:26-32
Impact factor: 4.572; Q1

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10. External Validation of Two Models to Predict Delirium in Critically Ill Adults Using Either the Confusion Assessment Method-ICU or the Intensive Care Delirium Screening Checklist for Delirium Assessment
Wassenaar A, Schoonhoven L, Devlin JW, van Haren FMP, Slooter AJC, Jorens PG, van der Jagt M, Simons KS, Egerod I, Burry LD, Beishuizen A, Matos J, Donders ART, Pickkers P, van den Boogaard M

Objectives: To externally validate two delirium prediction models (early prediction model for ICU delirium and recalibrated prediction model for ICU delirium) using either the Confusion Assessment Method-ICU or the Intensive Care Delirium Screening Checklist for delirium assessment.
Design: Prospective, multinational cohort study.
Setting: Eleven ICUs from seven countries in three continents.

Patients: Consecutive, delirium-free adults admitted to the ICU for greater than or equal to 6 hours in whom delirium could be reliably assessed.
Interventions: None.
Measurements and main results: The predictors included in each model were collected at the time of ICU admission (early prediction model for ICU delirium) or within 24 hours of ICU admission (recalibrated prediction model for ICU delirium). Delirium was assessed using the Confusion Assessment Method-ICU or the Intensive Care Delirium Screening Checklist. Discrimination was determined using the area under the receiver operating characteristic curve. The predictive performance was determined for the Confusion Assessment Method-ICU and Intensive Care Delirium Screening Checklist cohort, and compared with both prediction models' original reported performance. A total of 1,286 Confusion Assessment Method-ICU-assessed patients and 892 Intensive Care Delirium Screening Checklist-assessed patients were included. Compared with the area under the receiver operating characteristic curve of 0.75 (95% CI, 0.71-0.79) in the original study, the area under the receiver operating characteristic curve of the early prediction model for ICU delirium was 0.67 (95% CI, 0.64-0.71) for delirium as assessed using the Confusion Assessment Method-ICU and 0.70 (95% CI, 0.66-0.74) using the Intensive Care Delirium Screening Checklist. Compared with the original area under the receiver operating characteristic curve of 0.77 (95% CI, 0.74-0.79), the area under the receiver operating characteristic curve of the recalibrated prediction model for ICU delirium was 0.75 (95% CI, 0.72-0.78) for assessing delirium using the Confusion Assessment Method-ICU and 0.71 (95% CI, 0.67-0.75) using the Intensive Care Delirium Screening Checklist.
Conclusions: Both the early prediction model for ICU delirium and recalibrated prediction model for ICU delirium are externally validated using either the Confusion Assessment Method-ICU or the Intensive Care Delirium Screening Checklist for delirium assessment. Per delirium prediction model, both assessment tools showed a similar moderate-to-good statistical performance. These results support the use of either the early prediction model for ICU delirium or recalibrated prediction model for ICU delirium in ICUs around the world regardless of whether delirium is evaluated with the Confusion Assessment Method-ICU or Intensive Care Delirium Screening Checklist.

Gepubliceerd: Crit Care Med 2019 Oct;47(10):e827-e835
Impact factor: 6.971; Q1

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11. Predicting outcome in patients with moderate to severe traumatic brain injury using electroencephalography
Haveman ME, van Putten MJAM, Hom HW, Eertman-Meyer CJ, Beishuizen A, Tjepkema-Cloostermans MC

Background: Better outcome prediction could assist in reliable quantification and classification of traumatic brain injury (TBI) severity to support clinical decision-making. We developed a multifactorial model combining quantitative electroencephalography (qEEG) measurements and clinically relevant parameters as proof of concept for outcome prediction of patients with moderate to severe TBI.
Methods: Continuous EEG measurements were performed during the first 7 days of ICU admission. Patient outcome at 12 months was dichotomized based on the Extended Glasgow Outcome Score (GOSE) as poor (GOSE 1-2) or good (GOSE 3-

8). Twenty-three qEEG features were extracted. Prediction models were created using a Random Forest classifier based on qEEG features, age, and mean arterial blood pressure (MAP) at 24, 48, 72, and 96 h after TBI and combinations of two time intervals. After optimization of the models, we added parameters from the International Mission for Prognosis And Clinical Trial Design (IMPACT) predictor, existing of clinical, CT, and laboratory parameters at admission. Furthermore, we compared our best models to the online IMPACT predictor.
Results: Fifty-seven patients with moderate to severe TBI were included and divided into a training set (n = 38) and a validation set (n = 19). Our best model included eight qEEG parameters and MAP at 72 and 96 h after TBI, age, and nine other IMPACT parameters. This model had high predictive ability for poor outcome on both the training set using leave-one-out (area under the receiver operating characteristic curve (AUC) = 0.94, specificity 100%, sensitivity 75%) and validation set (AUC = 0.81, specificity 75%, sensitivity 100%). The IMPACT predictor independently predicted both groups with an AUC of 0.74 (specificity 81%, sensitivity 65%) and 0.84 (sensitivity 88%, specificity 73%), respectively.
Conclusions: Our study shows the potential of multifactorial Random Forest models using qEEG parameters to predict outcome in patients with moderate to severe TBI.

Gepubliceerd: Crit Care 2019 Dec 11;23(1):401
Impact factor: 6.959; Q1

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12. Methylprednisolone: Likely an Effective Treatment in Acute Respiratory Distress Syndrome
Meduri GU, Rochwerg B, Annane D, Pastores SM, Corticosteroid Guideline Task Force of SCCM and ESICM, includes Beishuizen A

Gepubliceerd: Crit Care Med 2019 Apr;47(4):e374-e375
Impact factor: 6.971; Q1

Totale impact factor: 148.288
Gemiddelde impact factor: 12.357

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 6.749
Gemiddelde impact factor: 3.375

Interne geneeskunde

1. Treatment of acute hepatitis C genotypes 1 and 4 with 8 weeks of grazoprevir plus elbasvir (DAHHS2): an open-label, multicentre, single-arm, phase 3b trial
Boerekamps A, De Weggheleire A, Van den Berk GE, Lauw FN, Claassen MAA, Posthouwer D, Bierman WF, Hullegie SJ, Popping S, van de Vijver DACM, Dofferhoff ASM, Kootstra GJ, Leyten EM, den Hollander J, Van Kasteren ME, Soetekouw R, Ammerlaan HSM, Schinkel J, Florence E, Arends JE, Rijnders BJA

Background: Direct-acting antivirals effectively treat chronic hepatitis C virus (HCV) infection but there is a paucity of data on their efficacy for acute HCV, when immediate treatment could prevent onward transmission. We assessed the efficacy of grazoprevir plus elbasvir treatment in acute HCV infection and investigated whether treatment can be shortened during the acute phase of HCV infection.
Methods: The Dutch Acute HCV in HIV study number 2 (DAHHS2) study was a single-arm, open-label, multicentre, phase 3b trial. Adult patients (>/=18 years) with acute HCV genotype 1 or 4 infection (duration of infection 26 weeks or less, according to presumed day of infection) were recruited at 15 HIV outpatient clinics in the Netherlands and Belgium. All patients were treated with 8 weeks of grazoprevir 100 mg plus elbasvir 50 mg administered as one oral fixed drug combination tablet once daily. The primary efficacy endpoint was sustained virological response at 12 weeks after the end of treatment (SVR12; HCV RNA <15 IU/mL) in all patients who started treatment. Reinfection with a different HCV virus was not considered treatment failure in the primary analysis. This trial is registered with ClinicalTrials.gov, number NCT02600325.
Findings: Between Feb 15, 2016, and March 2, 2018, we assessed 146 patients with a recently acquired HCV infection for eligibility, of whom 86 were enrolled and 80 initiated therapy, all within 6 months after infection. All patients who initiated treatment completed treatment and no patients were lost to follow-up. 79 (99%, 95% CI 93-100) of 80 patients achieved SVR12. All 14 patients who were infected with a virus carrying a clinically significant polymorphism in NS5A were cured. If reinfections were considered treatment failures, 75 (94%, 86-98) of 80 patients achieved SVR12. Two serious adverse events not considered related to the treatment were reported (traumatic rectal bleeding and low back surgery). The most common adverse event was a new sexually transmitted infection (19 [24%] of 80 patients). The most common reported possibly drug-related adverse events were fatigue (11 [14%] patients), headache (seven [9%] patients), insomnia (seven [9%] patients), mood changes (five [6%] patients), dyspepsia (five [6%] patients), concentration impairment (four [5%] patients), and dizziness (4 [5%] patients), all of which were regarded as mild by the treating physician. No adverse events led to study drug discontinuation.
Interpretation: 8 weeks of grazoprevir plus elbasvir was highly effective for the treatment of acute HCV genotype 1 or 4 infection. The ability to treat acute HCV immediately after diagnosis might help physicians to reach the WHO goal of HCV elimination by 2030.
Funding: Merck Sharp and Dohme and Health-Holland.

Gepubliceerd: Lancet Gastroenterol Hepatol 2019 Jan 16;4(4):269-77
Impact factor: 0; nvt

2. The effect of providing prescribing recommendations on appropriate prescribing: A cluster-randomized controlled trial in older adults in a preoperative setting
Boersma MN, Huibers CJA, Drenth-van Maanen AC, Emmelot-Vonk MH, Wilting I, Knol W

Aims: The Systematic Tool to Reduce Inappropriate Prescribing is a method to assess patient's medication and has been incorporated into a clinical decision support system: STRIP Assistant. Our aim was to evaluate the effect of recommendations generated using STRIP Assistant on appropriate prescribing and mortality in a preoperative setting.
Methods: This cluster-randomized controlled trial was carried out at the preoperative geriatric outpatient clinic. Residents who performed a comprehensive geriatric assessment were randomized to the control group and intervention group in a 1:1 ratio. Visiting patients aged 70 years or older on 5 or more medications were included.
Intervention: prescribing recommendations were generated by a physician using STRIP Assistant and given to the resident. Control group residents performed a medication review according to usual care.
Primary outcome: number of medication changes made because of potential prescribing omissions (PPOs), potentially inappropriate medications (PIMs), and suboptimal dosages according to the prescribing recommendations. Secondary outcome: 3-month postoperative mortality.
Results: 65 intervention and 59 control patients were included, attended by 34 residents. Significantly more medication changes because of PPOs and PIMs were made in the intervention group than in the control group (PPOs 26.2% vs 3.4%, odds ratio 0.04 [95% confidence interval 0.003-0.46] P < .05; PIMS 46.2% vs 15.3% odds ratio 0.14 [95% confidence interval 0.07-0.57] P < .005). There were no differences in dose adjustments or in postoperative mortality.
Conclusion: Prescribing recommendations generated with the help of STRIP Assistant improved appropriate prescribing in a preoperative geriatric outpatient clinic but did not affect postoperative mortality.

Gepubliceerd: Br J Clin Pharmacol 2019 Sep;85(9):1974-83
Impact factor: 3.867; Q1

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3. Metastatic Uveal Melanoma: Treatment Strategies and Survival-Results from the Dutch Melanoma Treatment Registry
Jochems A, van der Kooij MK, Fiocco M, Schouwenburg MG, Aarts MJ, van Akkooi AC, van den Berkmortel FWPJ, Blank CU, van den Eertwegh AJM, Franken MG, de Groot JB, Haanen JBAG, Hospers GAP, Koornstra RH, Kruit WHJ, Louwman M, Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije AJ, Vreugdenhil G, Wouters MWJM, van Zeijl MCT, van der Hoeven KJM, Kapiteijn E

Uveal melanoma (UM) is the most common primary intraocular tumor in adults. Up to 50% of UM patients will develop metastases. We present data of 175 metastatic UM patients diagnosed in the Netherlands between July 2012 and March 2018. In our cohort, elevated lactate dehydrogenase level (LDH) is an important factor associated

with poorer survival (Hazard Ratio (HR) 9.0, 95% Confidence Interval (CI) 5.63-14.35), and the presence of liver metastases is negatively associated with survival (HR 2.09, 95%CI 1.07-4.08). We used data from the nation-wide Dutch Melanoma Treatment Registry (DMTR) providing a complete overview of the location of metastases at time of stage IV disease. In 154 (88%) patients, the liver was affected, and only 3 patients were reported to have brain metastases. In 63 (36%) patients, mutation analysis was performed, showing a GNA11 mutation in 28.6% and a GNAQ mutation in 49.2% of the analyzed patients. In the absence of standard care of treatment options, metastatic UM patients are often directed to clinical trials. Patients participating in clinical trials are often subject to selection and usually do not represent the entire metastatic UM population. By using our nation-wide cohort, we are able to describe real-life treatment choices made in metastatic UM patients and 1-year survival rates in selected groups of patients.

Gepubliceerd: Cancers (Basel) 2019 Jul 18;11(7)
Impact factor: 6.162; Q1

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4. Feasibility and efficacy of addition of individualized dose lenalidomide to chlorambucil and rituximab as first-line treatment in elderly and FCR-unfit patients with advanced chronic lymphocytic leukemia

Kater AP, van Oers MHJ, van Norden Y, van der Straten L, Driessen J, Posthuma WFM, Schipperus M, Chamuleau MED, Nijland M, Doorduijn JK, Van Gelder M, Hoogendoorn M, De Croon F, Wittebol S, Kerst JM, Marijt EWA, Raymakers RAP, Schaafsma MR, Dobber JA, Kersting SA, Levin MD

Background: Lenalidomide (Len) has been proven effective both as monotherapy and in combination with rituximab for the treatment of chronic lymphocytic leukemia (CLL). Len has shown a distinct and more difficult to manage toxicity profile in the context of CLL, potentially hampering combination treatment with this drug.
Methods: In 1st-line CLL elderly and fludarabine, cyclophosphamide, rituximab (FCR) unfit patients, we conducted a phase 1-2 study to evaluate efficacy and safety of 6 cycles of chlorambucil (7mg/m2 on days 1-7), rituximab (375mg/m2 cycle 1 and 500mg/m2 cycle 2-6) and individual dosed Len (started on day 9 of cycle 1 2.5 mg, cycle 2 5 mg and cycle 3 and up 10 mg or maximum tolerated dose (MTD)) (induction-I). This was followed by 6 months of Len monotherapy at the MTD (induction-II). The primary endpoint was the overall response rate (ORR) after induction-I.
Results: Of 53 evaluable patients in phase 2, 47 patients (89%) completed induction-I and 36 patients (68%) completed induction-II. In an intention-to-treat analysis, the ORR was 83%. The median progression free survival (PFS) was 49 months, after a median follow-up time of 27 months. The 2- and 3-year PFS rate was 58% (standard error [SE]=8%) and 54% (SE=8%), respectively. The corresponding rate for OS was 98% (SE=2%) and 95% (SE=3%). No tumor lysis syndrome was observed, while tumor flair reaction occurred in 5 patients (9%, 1 grade 3). Most common hematologic toxicity was grade 3-4 neutropenia in 73%.
Conclusions: Addition of Len to a backbone of chlorambucil and rituximab followed by a fixed duration of Len monotherapy in 1st line elderly and FCR-unfit patients results in high remission rates and PFS rates, that seem comparable to those observed with novel combinations including novel CD20 monoclonal antibodies or

kinase inhibitors. Although Len-specific toxicity remains a concern, an individualized dose-escalation schedule is feasible and results in an acceptable toxicity profile.

Gepubliceerd: Haematologica 2019;104(1):147-54
Impact factor: 7.570; Q1

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5. The role of leptin and adiponectin as mediators in the relationship between adiposity and hand and knee osteoarthritis
Kroon FPB, Veenbrink AI, de Mutsert R, Visser AW, van Dijk KW, le Cessie S, Rosendaal FR, Kloppenburg M

Objectives: To investigate associations of leptin and adiponectin levels with knee and hand osteoarthritis, and explore whether these mediate the association between adiposity and osteoarthritis.
Methods: This is a cross-sectional analysis of baseline data from the population-based Netherlands Epidemiology of Obesity study. Adiposity was assessed with body mass index (BMI) and percentage total body fat (%TBF). Osteoarthritis, defined as hand or knee osteoarthritis, was determined using American College of Rheumatology criteria. Fasting serum adipokine levels were measured using immunoassays. Associations between adiposity and osteoarthritis were examined with logistic regression, adjusted for age, sex, ethnicity and education, and additionally for leptin and adiponectin as potential mediators.
Results: In 6408 participants (56% women, median age 56 years), prevalence of osteoarthritis was 22% (10% isolated knee and 8% isolated hand osteoarthritis). Leptin levels were positively associated with osteoarthritis, while adiponectin levels were not. Leptin partially mediated the association of adiposity with osteoarthritis (OR 1.40 (95%CI 1.30; 1.52) attenuated to 1.38 (1.24; 1.54) per 5 units BMI and OR 1.25 (1.17; 1.35) to 1.20 (1.10; 1.32) per 5 units %TBF, representing 4% and 17% mediation, respectively). Larger proportion mediation by leptin was found in knee (13%/27%) than in hand osteoarthritis (9%/18%). Sex-stratified analyses generally showed stronger associations between adiposity, leptin and osteoarthritis in women than in men.
Conclusions: Serum leptin levels were associated with osteoarthritis, and partially mediated the association between adiposity and osteoarthritis, while adiponectin levels were not associated with osteoarthritis. These findings provide evidence for systemic effects of adipose tissue in osteoarthritis.

Gepubliceerd: Osteoarthritis Cartilage 2019 Dec;27(12):1761-7
Impact factor: 4.879; Q1

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6. Caregivers' burden and fatigue during and after patients' treatment with concomitant chemoradiotherapy for locally advanced head and neck cancer: a prospective, observational pilot study
Langenberg SMCH, van Herpen CML, van Opstal CCM, Wymenga ANM, van der Graaf WTA, Prins JB

Purpose: Knowledge of caregivers' burden and fatigue before and after patients' treatment for locally advanced head and neck cancer is scarce. Therefore, we aimed

to explore caregivers' fatigue and burden in relation to patients' fatigue, distress, and quality of life.
Methods: For caregivers, burden and fatigue were assessed. For patients, fatigue severity, distress, and health-related quality of life (HRQoL) were assessed. Measurements were conducted prior to treatment, 1 week, and 3 months after chemoradiotherapy.
Results: Caregivers' burden and fatigue followed patients' high peak in distress, fatigue, and diminished HRQoL as a consequence of treatment. Caregivers' baseline fatigue was a predictor for fatigue after chemoradiotherapy. Female spouses with higher baseline levels of fatigue and burden and caring for patients with lower levels of HRQoL seem risk factors for burden after chemoradiotherapy.
Conclusions: Attention should be paid to caregivers' burden and fatigue before starting patients' intense treatment with chemoradiotherapy, as both burden and fatigue before starting treatment may contribute to burden and fatigue after chemoradiotherapy.

Gepubliceerd: Support Care Cancer 2019 Nov;27(11):4145-54
Impact factor: 2.754; Q1

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7. Caregivers of patients receiving long-term treatment with a tyrosine kinase inhibitor (TKI) for gastrointestinal stromal tumour (GIST): a cross-sectional assessment of their distress and burden
Langenberg SMCH, Reyners AKL, Wymenga ANM, Sieling GCM, Veldhoven CMM, van Herpen CML, Prins JB, van der Graaf WTA

Background: TKIs are a long-term treatment for GIST, and may have an impact on caregivers.
Material and methods: For this cross-sectional study, patients and caregivers were both included when patients had been treated with TKIs for at least six months. Caregivers completed questionnaires including demographics, distress (Hospital Anxiety and Depression scale), burden (Self-Perceived Pressure from Informal Care) general health (RAND-36), comorbidity (Self-administered Comorbidity Questionnaire), social support (Social Support List - Discrepancies) and marital satisfaction (Maudsley Marital Questionnaire). Patients completed similar questionnaires, without 'burden'. We conducted analyses to explore differences between caregivers with low/moderate versus high levels of burden and low versus high levels of distress.
Results: Sixty-one out of seventy-one eligible couples (84%) were included in the analysis. The median age of the caregivers was 60 years; 66% were female and 78% were the patients' spouse. The median age of the patients was 66 years; 43% were female. Caregivers experienced high levels of burden and distress in 10% and 23%, respectively. Caregivers with high levels of burden perceived significantly lower mental health, less vitality, lower general health and high levels of distress. Significantly higher levels of burden were found in non-spouses, caregivers of patients with more treatment-related side-effects, caregivers who spent more hours caring, and those caring for more than one person. For distress, caregivers with high levels of distress perceived significantly more burden, lower social functioning, more role physical and emotional problems, lower mental health, less vitality and lower

general health. Furthermore, high levels of distress were found in caregivers of more dependent patients and those caring for more than one person.
Conclusions: Caregivers of the patients with GIST treated with TKI are managing well. There is a small, vulnerable group of caregivers with high levels of burden and/or distress, show more health-related problems, both physical and mental, and require adequate support.

Gepubliceerd: Acta Oncol 2019 Feb;58(2):191-9
Impact factor: 3.298; Q2

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8. Bortezomib-based induction followed by stem cell transplantation in light chain amyloidosis: results of the multicenter HOVON 104 trial
Minnema MC, Nasserinejad K, Hazenberg B, Hegenbart U, Vlummens P, Ypma PF, Kroger N, Wu KL, Kersten MJ, Schaafsma MR, Croockewit S, de Waal E, Zweegman S, Tick L, Broijl A, Koene H, Bos G, Sonneveld P, Schonland S

This prospective, multicenter, phase II study investigated the use of four cycles of bortezomib-dexamethasone induction treatment, followed by high-dose melphalan and autologous stem cell transplantation (SCT) in patients with newly diagnosed light chain amyloidosis. The aim of the study was to improve the hematologic complete remission (CR) rate 6 months after SCT from 30% to 50%. Fifty patients were enrolled and 72% had two or more organs involved. The overall hematologic response rate after induction treatment was 80% including 20% CR and 38% very good partial remissions (VGPR). Fifteen patients did not proceed to SCT for various reasons but mostly treatment-related toxicity and disease-related organ damage and death (2 patients). Thirty-one patients received melphalan 200 mg/m(2) and four patients a reduced dose because of renal function impairment. There were no deaths related to the transplantation procedure. Hematologic responses improved at 6 months after SCT to 86% with 46% CR and 26% VGPR. However, due to the high treatment discontinuation rate before transplantation the primary endpoint of the study was not met and the CR rate in the intention-to-treat analysis was 32%. Organ responses continued to improve after SCT. We confirm the high efficacy of bortezomib-dexamethasone treatment in patients with AL amyloidosis. However, because of both treatment-related toxicity and disease characteristics, 30% of the patients could not proceed to SCT after induction treatment. (Trial registered at Dutch Trial Register identifier NTR3220).

Gepubliceerd: Haematologica 2019 Nov;104(11):2274-82
Impact factor: 7.570; Q1

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9. Screening and Stepped Care Targeting Psychological Distress in Patients With Metastatic Colorectal Cancer: The TES Cluster Randomized Trial
Schuurhuizen CSEW, Braamse AMJ, Beekman ATF, Cuijpers P, van der Linden MHM, Hoogendoorn AW, Berkhof H, Sommeijer DW, Lustig V, Vrijaldenhoven S, Bloemendal HJ, van Groeningen CJ, van Zweeden AA, van der Vorst MJDL, Rietbroek R, Tromp-van Driel CS, Wymenga MNW, van der Linden PW, Beeker A, Polee MB, Batman E, Los M, van Bochove A, Brakenhoff JAC, Konings IRHM, Verheul HMW, Dekker J

Background: This study evaluated the effectiveness of a screening and stepped care program (the TES program) in reducing psychological distress compared with care as usual (CAU) in patients with metastatic colorectal cancer starting with first-line systemic palliative treatment.
Patients and methods: In this cluster randomized trial, 16 hospitals were assigned to the TES program or CAU. Patients in the TES arm were screened for psychological distress with the Hospital Anxiety and Depression Scale and the Distress Thermometer/Problem List (at baseline and 10 and 18 weeks). Stepped care was offered to patients with distress or expressed needs, and it consisted of watchful waiting, guided self-help, face-to-face problem-solving therapy, or referral to specialized mental healthcare. The primary outcome was change in psychological distress over time, and secondary outcomes were quality of life, satisfaction with care, and recognition and referral of distressed patients by clinicians. Linear mixed models and effect sizes were used to evaluate differences.
Results: A total of 349 patients were randomized; 184 received the TES program and 165 received CAU. In the TES arm, 60.3% of the patients screened positive for psychological distress, 26.1% of which entered the stepped care program (14.7% used only watchful waiting and 11.4% used at least one of the other treatment steps). The observed low use of the TES program led us to pursue a futility analysis, which showed a small conditional power and therefore resulted in halted recruitment for this study. No difference was seen in change in psychological distress over time between the 2 groups (effect size, -0.16; 95% CI, -0.35 to 0.03; P>.05). The TES group reported higher satisfaction with the received treatment and better cognitive quality of life (all P<.05).
Conclusions: As a result of the low use of stepped care, a combined screening and treatment program targeting psychological distress in patients with metastatic colorectal cancer did not improve psychological distress. Our results suggest that enhanced evaluation of psychosocial concerns may improve aspects of patient well-being.

Gepubliceerd: J Natl Compr Canc Netw 2019 Aug 1;17(8):911-20
Impact factor: 7.570; Q1

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10. Insulin-like factor 3, luteinizing hormone and testosterone in testicular cancer patients: effects of beta-hCG and cancer treatment
Steggink LC, van Beek AP, Boer H, Meijer C, Lubberts S, Oosting SF, de Jong IJ, van Ginkel RJ, Lefrandt JD, Gietema JA, Nuver J

Background: Primary hypogonadism (low testosterone and high luteinizing hormone, LH) is present in approximately 20% of testicular cancer (TC) survivors after orchidectomy with or without chemotherapy.
Objectives: We investigated insulin-like factor 3 (INSL3), a novel marker of Leydig cell function, in TC patients.
Materials and Methods: We analyzed: (I) a cross-sectional cohort of TC patients after orchidectomy with or without chemotherapy (1988-1999) at long-term follow-up (median 36 and 35 years of age at follow-up, respectively) and healthy men of similar age; (II) a longitudinal cohort of chemotherapy-treated TC patients (2000-2008), analyzed before and 1 year after chemotherapy (median 29 years of age at

chemotherapy). INSL3, testosterone, and LH were compared between groups and over time and related to pre-chemotherapy beta-hCG levels.
Results: In the cross-sectional cohort, TC patients at median 7 years after orchidectomy and chemotherapy (n = 79) had higher LH (p < 0.001), lower testosterone (p = 0.001), but similar INSL3 as controls (n = 40). After orchidectomy only (n = 25), higher LH (p = 0.02), but no differences in testosterone or INSL3 were observed compared to controls. In the longitudinal cohort, patients with normal pre-chemotherapy beta-hCG (</=5 mU/L, n = 35) had increased LH 1 year after chemotherapy compared to pre-chemotherapy (p = 0.001), and no change in testosterone or INSL3. In contrast, patients with high beta-hCG pre-chemotherapy (n = 42) had suppressed LH, markedly elevated testosterone, and low INSL3 at start of chemotherapy, with increased LH, decreased testosterone, and increased INSL3 1 year later (all p < 0.001).
Discussion: Changes in LH show that gonadal endocrine function is disturbed before chemotherapy, 1 year later, and at long-term follow-up in chemotherapy-treated TC patients.
Conclusion: Pre-chemotherapy, beta-hCG-producing tumors affect the gonadal endocrine axis, demonstrated by increased testosterone and decreased LH. INSL3 did not uniformly follow the pattern of testosterone.

Gepubliceerd: Andrology 2019 Jul;7(4):441-8
Impact factor: 3.106; Q1

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11. Cardiac Function After Radiation Therapy for Breast Cancer
van den Bogaard VAB, van Luijk P, Hummel YM, van der Meer P, Schuit E, Boerman LM, Maass SWMC, Nauta JF, Steggink LC, Gietema JA, de Bock GH, Berendsen AJ, Smit WGJM, Sijtsema NM, Kierkels RGJ, Langendijk JA, Crijns APG, Maduro JH

Purpose: The main purpose of this study was to test the hypothesis that incidental cardiac irradiation is associated with changes in cardiac function in breast cancer (BC) survivors treated with radiation therapy (RT).
Methods and materials: We conducted a cross-sectional study consisting of 109 BC survivors treated with RT between 2005 and 2011. The endpoint was cardiac function, assessed by echocardiography. Systolic function was assessed with the left ventricular ejection fraction (LVEF) (n = 107) and the global longitudinal strain (GLS) of the left ventricle (LV) (n = 52). LV diastolic dysfunction (n = 109) was defined by e' at the lateral and septal region, which represents the relaxation velocity of the myocardium. The individual calculated RT dose parameters of the LV and coronary arteries were collected from 3-dimensional computed tomography-based planning data. Univariable and multivariable analysis using forward selection was performed to identify the best predictors of cardiac function. Robustness of selection was assessed using bootstrapping. The resulting multivariable linear regression model was presented for the endpoints of systolic and diastolic function.
Results: The median time between BC diagnosis and echocardiography was 7 years. No relation between RT dose parameters and LVEF was found. In the multivariable analysis for the endpoint GLS of the LV, the maximum dose to the left main coronary artery was most often selected across bootstrap samples. For decreased diastolic function, the most often selected model across bootstrap samples included age at

time of BC diagnosis and hypertension at baseline. Cardiac dose-volume histogram parameters were less frequently selected for this endpoint.
Conclusions: This study shows an association between individual cardiac dose distributions and GLS of the LV after RT for BC. No relation between RT dose parameters and LVEF was found. Diastolic function was most associated with age and hypertension at time of BC diagnosis. Further research is needed to make definitive conclusions.

Gepubliceerd: Int J Radiat Oncol Biol Phys 2019 Jun 1;104(2):392-400
Impact factor: 6.203; Q1

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12. Clinical and Molecular Characteristics May Alter Treatment Strategies of Thyroid Malignancies in DICER1-syndrome
van der Tuin K, de Kock L, Kamping EJ, Hannema SE, Pouwels MM, Niedziela M, van Wezel T, Hes FJ, Jongmans MC, Foulkes WD, Morreau H

Context: The DICER1 syndrome is a rare, autosomal dominant inherited disorder that predisposes to a variety of cancerous and noncancerous tumors of mostly pediatric- and adolescent-onset, including differentiated thyroid carcinoma (DTC). DICER1-related DTC has been hypothesized to arise secondary to the increased prevalence of pre-malignant lesions, i.e. thyroid hyperplastic nodules.
Objective: To determine somatic alterations in DICER1-associated differentiated thyroid cancer and to study patient outcomes.
Design: Retrospective series.
Setting: Tertiary referral centers. Patients: Ten patients with germline pathogenic DICER1 variants and early-onset DTC. Investigation: Somatic DICER1 mutation analysis and extensive somatic DNA variant and gene fusion analyses on all tumors.
Results: Median age at DTC diagnosis was 13.5 years and no patients developed recurrent or metastatic disease (median follow-up 8 years). All thyroid specimens showed diffuse nodular hyperplasia with at least one focus suspect for DTC, but without infiltrative growth, extra-thyroidal extension, vascular invasion, or lymph node metastasis. Distinct somatic DICER1 RNase IIIb domain variants were identified in most presumed-malignant (and benign) nodules tested from each patient's tumor, suggestive of multiple distinct poly-clonal tumors. Furthermore, 9 of 10 DICER1-related DTC lacked well known oncogenic driver DNA variants and gene rearrangements. **Conclusions:** On the basis of our clinical, histological and molecular data, we consider that the majority of DICER1-related DTCs form a low-risk subgroup. As these tumors may arise from one of many benign polyclonal nodules, hemi- or more likely total thyroidectomy may be often required, but radioiodine treatment may be unnecessary, given the patients age and their low propensity for metastases.

Gepubliceerd: J Clin Endocrinol Metab 2019;104(2):277-84
Impact factor: 5.605; Q1

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13. Optimising pharmacotherapy in older cancer patients with polypharmacy
Vrijkorte E, de Vries J, Schaafsma R, Wymenga M, Oude Munnink T

Objective: Polypharmacy is frequent among older cancer patients and increases the risk of potential drug-related problems (DRPs). DRPs are associated with adverse drug events, drug-drug interactions and hospitalisations. Since no standardised polypharmacy assessment methods for oncology patients exist, we aimed to develop one that can be integrated into routine care.
Methods: Based on the Systematic Tool to Reduce Inappropriate Prescribing (STRIP), we developed OncoSTRIP, which includes a polypharmacy anamnesis, a concise geriatric assessment, a polypharmacy analysis taking life expectancy into account and an optimised treatment plan. Patients >/=65 years with >/=5 chronic drugs visiting our outpatient oncology clinic were eligible for the polypharmacy assessment.
Results: OncoSTRIP was integrated into routine care of our older cancer patients. In 47 of 60 patients (78%), potential DRPs (n = 101) were found. In total, 85 optimisations were recommended, with an acceptance rate of 41%. It was possible to reduce the number of potential DRPs by 41% and the number of patients with at least one potential DRP by 30%. Mean time spent per patient was 71 min.
Conclusions: Polypharmacy assessment of older cancer patients identifies many pharmacotherapeutic optimisations. With OncoSTRIP, polypharmacy assessments can be integrated into routine care.

Gepubliceerd: Eur J Cancer Care (Engl) 2019 Nov 6;e13185
Impact factor: 2.421; Q1

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14. Perioperative systemic therapy and cytoreductive surgery with HIPEC versus upfront cytoreductive surgery with HIPEC alone for isolated resectable colorectal peritoneal metastases: protocol of a multicentre, open-label, parallel-group, phase II-III, randomised, superiority study (CAIRO6)
Rovers KP, Bakkers C, Simkens GAAM, Burger JWA, Nienhuijs SW, Creemers GM, Thijs AMJ, Brandt-Kerkhof ARM, Madsen EVE, Ayez N, de Boer NL, van Meerten E, Tuynman JB, Kusters M, Sluiter NR, Verheul HMW, van der Vliet HJ, Wiezer MJ, Boerma D, Wassenaar ECE, Los M, Hunting CB, Aalbers AGJ, Kok NFM, Kuhlmann KFD, Boot H, Chalabi M, Kruijff S, Been LB, van Ginkel RJ, de Groot DJA, Fehrmann RSN, de Wilt JHW, Bremers AJA, de Reuver PR, Radema SA, Herbschleb KH, van Grevenstein WMU, Witkamp AJ, Koopman M, Haj Mohammad N, van Duyn EB, Mastboom WJB, Mekenkamp LJM, Nederend J, Lahaye MJ, Snaebjornsson P, Verhoef C, van Laarhoven HWM, Zwinderman AH, Bouma JM, Kranenburg O, van 't Erve I, Fijneman RJA, Dijkgraaf MGW, Hemmer PHJ, Punt CJA, Tanis PJ, de Hingh IHJT

Background: Upfront cytoreductive surgery with HIPEC (CRS-HIPEC) is the standard treatment for isolated resectable colorectal peritoneal metastases (PM) in the Netherlands. This study investigates whether addition of perioperative systemic therapy to CRS-HIPEC improves oncological outcomes.
Methods: This open-label, parallel-group, phase II-III, randomised, superiority study is performed in nine Dutch tertiary referral centres. Eligible patients are adults who have a good performance status, histologically or cytologically proven resectable PM of a colorectal adenocarcinoma, no systemic colorectal metastases, no systemic therapy for colorectal cancer within six months prior to enrolment, and no previous CRS-HIPEC. Eligible patients are randomised (1:1) to perioperative systemic therapy

and CRS-HIPEC (experimental arm) or upfront CRS-HIPEC alone (control arm) by using central randomisation software with minimisation stratified by a peritoneal cancer index of 0-10 or 11-20, metachronous or synchronous PM, previous systemic therapy for colorectal cancer, and HIPEC with oxaliplatin or mitomycin C. At the treating physician's discretion, perioperative systemic therapy consists of either four 3-weekly neoadjuvant and adjuvant cycles of capecitabine with oxaliplatin (CAPOX), six 2-weekly neoadjuvant and adjuvant cycles of 5-fluorouracil/leucovorin with oxaliplatin (FOLFOX), or six 2-weekly neoadjuvant cycles of 5-fluorouracil/leucovorin with irinotecan (FOLFIRI) followed by four 3-weekly (capecitabine) or six 2-weekly (5-fluorouracil/leucovorin) adjuvant cycles of fluoropyrimidine monotherapy. Bevacizumab is added to the first three (CAPOX) or four (FOLFOX/FOLFIRI) neoadjuvant cycles. The first 80 patients are enrolled in a phase II study to explore the feasibility of accrual and the feasibility, safety, and tolerance of perioperative systemic therapy. If predefined criteria of feasibility and safety are met, the study continues as a phase III study with 3-year overall survival as primary endpoint. A total of 358 patients is needed to detect the hypothesised 15% increase in 3-year overall survival (control arm 50%; experimental arm 65%). Secondary endpoints are surgical characteristics, major postoperative morbidity, progression-free survival, disease-free survival, health-related quality of life, costs, major systemic therapy related toxicity, and objective radiological and histopathological response rates.
Discussion: This is the first randomised study that prospectively compares oncological outcomes of perioperative systemic therapy and CRS-HIPEC with upfront CRS-HIPEC alone for isolated resectable colorectal PM.
Trial Registration: Clinicaltrials.gov/ NCT02758951 , NTR/ NTR6301 , ISRCTN/ ISRCTN15977568 , EudraCT/ 2016-001865-99.

Gepubliceerd: BMC Cancer 2019 Apr 25;19(1):390
Impact factor: 2.933; Q3

Totale impact factor: 63.938
Gemiddelde impact factor: 4.567

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 11.852
Gemiddelde impact factor: 3.951

Kindergeneeskunde

1. Are serum ferritin and transferrin saturation risk markers for restless legs syndrome in young adults? Longitudinal and cross-sectional data from the Western Australian Pregnancy Cohort (Raine) Study
Lammers N, Curry-Hyde A, Smith AJ, Eastwood PR, Straker LM, Champion D, McArdle N

Restless legs syndrome has been associated with serum iron deficiency in clinical studies. However, studies investigating this relationship have had inconsistent results and there are no studies in young adults. Therefore, we investigated the relationship between serum measures of iron stores and restless legs syndrome in young adults in the community. Participants in the Western Australian Pregnancy Cohort (Raine) Study answered questions on restless legs syndrome (n = 1,100, 54% female) at age 22 years, and provided serum measures of iron stores (ferritin and transferrin saturation) at ages 17 and 22 years. Restless legs syndrome was diagnosed when four International RLS Study Group criteria were met (urge to move, dysaesthesia, relief by movement, worsening during evening/night) and these symptoms occurred >/=5 times per month. Logistic regression was used to assess associations between serum iron stores and restless legs syndrome, adjusting for potential confounders. The prevalence of restless legs syndrome at age 22 years was 3.0% (n = 33, 70% female). Among those who provided restless legs syndrome and iron data at age 22 years (n = 865), the median (interquartile range) ferritin was not different between the restless legs syndrome (55 [29.5-103.5] microg L(-1)) and the non-restless legs syndrome group (65.0 [35.0-103.3] microg L(-1) , p = 0.2), nor were there differences in iron deficiency prevalence (p = 0.36). There was no association between restless legs syndrome (22 years) and iron stores (17, 22 years) before or after adjustment for potential confounders. There was no association between restless legs syndrome at 22 years and iron stores at 17 or 22 years in this cohort. Serum iron stores may not be a useful indicator of restless legs syndrome risk in young adults in the community.

Gepubliceerd: J Sleep Res 2019 Oct;28(5):e12741
Impact factor: 3.432; Q2

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2. Assessing Exercise-Induced Bronchoconstriction in Children; The Need for Testing
Lammers N, van Hoesel MHT, Kamphuis M, Brusse-Keizer M, van der Palen J, Visser R, Thio BJ, Driessen JMM

Objective: Exercise-induced bronchoconstriction (EIB) is a specific morbidity of childhood asthma and a sign of insufficient disease control. EIB is diagnosed and monitored based on lung function changes after a standardized exercise challenge test (ECT). In daily practice however, EIB is often evaluated with self-reported respiratory symptoms and spirometry. We aimed to study the capacity of pediatricians to predict EIB based on information routinely available during an outpatient clinic visit. **Methods:** A clinical assessment was performed in 20 asthmatic children (mean age 11.6 years) from the outpatient clinic of the MST hospital from May 2015 to July 2015. During this assessment, video images were made. EIB was measured with a

standardized ECT performed in cold, dry air. Twenty pediatricians (mean years of experience 14.4 years) each evaluated five children, providing 100 evaluations, and predicted EIB severity based on their medical history, physical examination, and video images. EIB severity was predicted again after additionally providing baseline spirometry results.
Results: Nine children showed no EIB, four showed mild EIB, two showed moderate, and five showed severe EIB. Based on clinical information and spirometry results, pediatricians detected EIB with a sensitivity of 84% (95% CI 72-91%) and a specificity of 24% (95% CI 14-39%).The agreement between predicted EIB severity classifications and the validated classifications after the ECT was slight [Kappa = 0.05 (95% CI 0.00-0.17)]. This agreement still remained slight when baseline spirometry results were provided [Kappa = 0.19 (95% CI 0.06-0.32)].
Conclusion: Pediatricians' prediction of EIB occurrence was sensitive, but poorly specific. The prediction of EIB severity was poor. Pediatricians should be aware of this in order to prevent misjudgement of EIB severity and disease control.

Gepubliceerd: Front Pediatr 2019;7:157
Impact factor: 2.349; Q2

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3. Does exercise-induced bronchoconstriction affect physical activity patterns in asthmatic children?
van der Kamp MR, Thio BJ, Tabak M, Hermens HJ, Driessen J, van der Palen J

Exercise-induced bronchoconstriction (EIB) is a sign of uncontrolled childhood asthma and classically occurs after exercise. Recent research shows that EIB frequently starts during exercise, called breakthrough-EIB (BT-EIB). It is unknown whether this more severe type of EIB forces children to adapt their physical activity (PA) pattern in daily life. Therefore, this pilot study aims to investigate daily life PA (amount, intensity, duration, and distribution) in children with BT-EIB, 'classic' EIB, and without EIB. A Fitbit Zip activity tracker was used for one week to objectively measure daily life PA at one-minute intervals. Thirty asthmatic children participated. Children with BT-EIB were less physically active compared to children without EIB (respectively 7994 and 11,444 steps/day, $p = .02$). Children with BT-EIB showed less moderate-to-vigorous PA compared to the children without (respectively 117 and 170 minutes/day, $p = .02$). Children with EIB (both BT and classic) had significant shorter bouts of activity and a less stretched distribution of bout lengths compared to the non-EIB group (all $p < .05$). These results emphasize a marked association between EIB severity and PA patterns in daily life, stressing the need for a thorough clinical evaluation of exercise-induced symptoms in childhood asthma.

Gepubliceerd: J Child Health Care 2019 Oct 13;1367493519881257
Impact factor: 1.505; Q2

Totale impact factor: 7.286
Gemiddelde impact factor: 2.429

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 7.286

Gemiddelde impact factor: 2.429

Klinische chemie

1. Immunophenotypic measurable residual disease (MRD) in acute myeloid leukemia: Is multicentric MRD assessment feasible?
Brooimans RA, van der Velden VHJ, Boeckx N, Slomp J, Preijers F, Te Marvelde JG, Van Ngoc M, Heijs A, Huys E, van der Holt B, de Greef GE, Kelder A, Schuurhuis GJ

Flow-cytometric detection of now termed measurable residual disease (MRD) in acute myeloid leukemia (AML) has proven to have an independent prognostic impact. In a previous multicenter study we developed protocols to accurately define leukemia-associated immunophenotypes (LAIPs) at diagnosis. It has, however, not been demonstrated whether the use of the defined LAIPs in the same multicenter setting results in a high concordance between centers in MRD assessment. In the present paper we evaluated whether interpretation of list-mode data (LMD) files, obtained from MRD assessment of previously determined LAIPs during and after treatment, could reliably be performed in a multicenter setting. The percentage of MRD positive cells was simultaneously determined in totally 173 LMD files from 77 AML patients by six participating centers. The quantitative concordance between the six participating centers was meanly 84%, with slight variation of 75%-89%. In addition our data showed that the type and number of LAIPs were of influence on the performance outcome. The highest concordance was observed for LAIPs with cross-lineage expression, followed by LAIPs with an asynchronous antigen expression. Our results imply that immunophenotypic MRD assessment in AML will only be feasible when fully standardized methods are used for reliable multicenter assessment.

Gepubliceerd: Leuk Res 2019 Jan;76:39-47
Impact factor: 2.066; Q3

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2. Retrospective analysis of repeated dexamethasone suppression tests - the added value of measuring dexamethasone
de Graaf AJ, Mulder AL, Krabbe JG

Gepubliceerd: Ann Clin Biochem 2019 Nov;56(6):708-10
Impact factor: 1.893; Q3

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3. A Multicenter Comparison of 2 Point-of-Care Activated Clotting Time Test Systems
Kemna EWM, Schellings MWM, Vlachojannis GJ, Falter F, Milane-Santman A, Hesselink T, Scholten M, Krabbe JG

Gepubliceerd: J Appl Lab Med 2019 Nov;4(3):468-70
Impact factor: 0; nvt

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4. CD34(+)CD38(-) leukemic stem cell frequency to predict outcome in acute myeloid leukemia

Zeijlemaker W, Grob T, Meijer R, Hanekamp D, Kelder A, Carbaat-Ham JC, Oussoren-Brockhoff YJM, Snel AN, Veldhuizen D, Scholten WJ, Maertens J, Breems DA, Pabst T, Manz MG, van der Velden VHJ, Slomp J, Preijers F, Cloos J, van de Loosdrecht AA, Lowenberg B, Valk PJM, Jongen-Lavrencic M, Ossenkoppele GJ, Schuurhuis GJ

Current risk algorithms are primarily based on pre-treatment factors and imperfectly predict outcome in acute myeloid leukemia (AML). We introduce and validate a post-treatment approach of leukemic stem cell (LSC) assessment for prediction of outcome. LSC containing CD34+CD38- fractions were measured using flow cytometry in an add-on study of the HOVON102/SAKK trial. Predefined cut-off levels were prospectively evaluated to assess CD34+CD38-LSC levels at diagnosis (n = 594), and, to identify LSC^{low}/LSC^{high} (n = 302) and MRD^{low}/MRD^{high} patients (n = 305) in bone marrow in morphological complete remission (CR). In 242 CR patients combined MRD and LSC results were available. At diagnosis the $CD34^{+}CD38^{-}$ LSC frequency independently predicts overall survival (OS). After achieving CR, combining LSC and MRD showed reduced survival in MRD^{high}/LSC^{high} patients (hazard ratio [HR] 3.62 for OS and 5.89 for cumulative incidence of relapse [CIR]) compared to MRD^{low}/LSC^{high}, MRD^{high}/LSC^{low}, and especially MRD^{low}/LSC^{low} patients. Moreover, in the NPM1mutant positive sub-group, prognostic value of golden standard NPM1-MRD by qPCR can be improved by addition of flow cytometric approaches. This is the first prospective study demonstrating that LSC strongly improves prognostic impact of MRD detection, identifying a patient subgroup with an almost 100% treatment failure probability, warranting consideration of LSC measurement incorporation in future AML risk schemes.

Gepubliceerd: Leukemia 2019;33(5):1102-12
Impact factor: 9.944; Q1

Totale impact factor: 13.903
Gemiddelde impact factor: 3.476

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 1.893
Gemiddelde impact factor: 0.947

Klinische farmacie

1. Maternal paracetamol intake and fetal ductus arteriosus constriction or closure: a case series analysis
Allegaert K, Mian P, Lapillonne A, van den Anker JN

Recent case reports describe an association between maternal paracetamol intake and fetal ductus arteriosus constriction or closure. To put these cases into perspective and explore causality, a structured literature search was conducted. The World Health Organization Uppsala Monitoring Centre (WHO-UMC) causality tool was applied to the cases retrieved. The search resulted in 12 papers with 25 case descriptions, of which one case was classified as unlikely, nine as possible, 11 as probable and four as certain. Consequently, we concluded that a causal relationship between maternal paracetamol intake and fetal ductus arteriosus constriction or closure is likely. These findings suggest that pharmacovigilance studies on paracetamol safety during pregnancy are warranted to quantify the event and put the current findings into clinical perspective. Although analgesia during pregnancy and during the peripartum period is of obvious relevance, alternative analgesics such as opioids or other nonsteroidal anti-inflammatory drugs also have side effects.

Gepubliceerd: Br J Clin Pharmacol 2019 Jan;85(1):245-51
Impact factor: 3.867; Q1

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2. Clinical Pharmacokinetic Studies in Pregnant Women and the Relevance of Pharmacometric Tools
Dallmann A, Mian P, Van den Anker J, Allegaert K

Background: In clinical pharmacokinetic (PK) studies, pregnant women are significantly underrepresented because of ethical and legal reasons which lead to a paucity of information on potential PK changes in this population. As a consequence, pharmacometric tools became instrumental to explore and quantify the impact of PK changes during pregnancy.
Methods: We explore and discuss the typical characteristics of population PK and physiologically based pharmacokinetic (PBPK) models with a specific focus on pregnancy and postpartum.
Results: Population PK models enable the analysis of dense, sparse or unbalanced data to explore covariates in order to (partly) explain inter-individual variability (including pregnancy) and to individualize dosing. For population PK models, we subsequently used an illustrative approach with ketorolac data to highlight the relevance of enantiomer specific modeling for racemic drugs during pregnancy, while data on antibiotic prophylaxis (cefazolin) during surgery illustrate the specific characteristics of the fetal compartments in the presence of timeconcentration profiles. For PBPK models, an overview on the current status of reports and papers during pregnancy is followed by a PBPK cefuroxime model to illustrate the added benefit of PBPK in evaluating dosing regimens in pregnant women.
Conclusions: Pharmacometric tools became very instrumental to improve perinatal pharmacology. However, to reach their full potential, multidisciplinary collaboration and structured efforts are needed to generate more information from already available

datasets, to share data and models, and to stimulate cross talk between clinicians and pharmacometricians to generate specific observations (pathophysiology during pregnancy, breastfeeding) needed to further develop the field.

Gepubliceerd: Curr Pharm Des 2019;25(5):483-95
Impact factor: 2.412; Q3

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3. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment
Krens SD, Lassche G, Jansman FGA, Desar IME, Lankheet NAG, Burger DM, van Herpen CML, van Erp NP

Renal or hepatic impairment is a common comorbidity for patients with cancer either because of the disease itself, toxicity of previous anticancer treatments, or because of other factors affecting organ function, such as increased age. Because renal and hepatic function are among the main determinants of drug exposure, the pharmacokinetic profile might be altered for patients with cancer who have renal or hepatic impairment, necessitating dose adjustments. Most anticancer drugs are dosed near their maximum tolerated dose and are characterised by a narrow therapeutic index. Consequently, selecting an adequate dose for patients who have either hepatic or renal impairment, or both, is challenging and definitive recommendations on dose adjustments are scarce. In this Review, we discuss the effect of renal and hepatic impairment on the pharmacokinetics of anticancer drugs. To guide clinicians in selecting appropriate dose adjustments, information from available drug labels and from the published literature were combined to provide a practical set of recommendations for dose adjustments of 160 anticancer drugs for patients with hepatic and renal impairment.

Gepubliceerd: Lancet Oncol 2019 Apr;20(4):e200-e207
Impact factor: 35.386; Q1

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4. Use of the Child-Pugh score in anticancer drug dosing decision making: proceed with caution - Authors' reply
Krens SD, Lassche G, Jansman FGA, Desar IME, Lankheet NAG, Burger DM, van Herpen CML, van Erp NP

Gepubliceerd: Lancet Oncol 2019 Jun;20(6):e290
Impact factor: 35.386; Q1

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5. Effects of European Society of Cardiology guidelines on medication profiles after hospitalization for heart failure in 22,476 Dutch patients: from 2001 until 2015
Kruik-Kolloffel WJ, Linssen GCM, Kruik HJ, Movig KLL, Heintjes EM, van der Palen J

Prescriber adherence to guideline-recommended medication in patients with heart failure (HF) in clinical practice is suboptimal. We analyzed how evolving guideline recommendations influenced medication profiles after a first HF hospitalization. We

extracted medication profiles from the Dutch PHARMO Database Network for 22,476 patients with a diagnosis of HF at hospital discharge between 2001 and 2015. The percentage of patients prescribed the combination of a beta-blocker (BB) and an angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB) increased from 24 to approximately 45% within this 15-year period. The percentage of patients who also used a mineralocorticoid-receptor antagonist (MRA) reached approximately 20%. The probability of being prescribed these combinations decreased with increasing age. As a consequence of the policy change in the ESC guideline 2001, the use of BB increased from less than 40% in 2001 to about 70% by 2015. The percentage of patients prescribed an ACEI and/or an ARB, an MRA, or a diuretic was about stable, at respectively 63%, 37%, and 82%. Although the 2012 ESC guideline also advised MRA in the New York Heart Association (NYHA) class II, there was no increase in MRA prescriptions. Compliance with the ESC guidelines varied for the individual recommendations. Remarkably, there was no significant increase in MRA prescriptions. At the same time, developments were demonstrated, which were not instigated by the guidelines, like the shift from ACEI to ARB. Although the exact HF classification of our patients was unknown, given a relatively stable case mix, our data provide insight into "real-world" pharmacological management.

Gepubliceerd: Heart Fail Rev 2019 Jul;24(4):499-510
Impact factor: 4.015; Q2

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6. High levels of several antipsychotics and antidepressants due to a pharmacogenetic cause: a case report
Mian P, Somers M, Berg MT, Cahn W, Wilting I, Schaik RV

Pharmacogenetic analysis to explain or predict the response of a specific patient to drug therapy is increasingly used in clinical practice. This holds especially true for CYP genotyping in psychiatry. We present a patient with genetic polymorphisms in more than one CYP450 enzyme, resulting in reduced effectiveness of CYP enzymes, explaining the high drug serum trough levels of antipsychotics and antidepressants and difficulty in optimizing therapy and dosing. Mrs X was found to be a CYP1A2, CYP2D6, CYP3A4 intermediate and in addition a CYP2C19 poor metabolizer. For Mrs X, pharmacogenetic analysis has contributed to reconsider choice and use of medication. Prior knowledge of the genetic polymorphisms in this patient might have avoided treatment delay and discomfort.

Gepubliceerd: Pharmacogenomics 2019 Jun;20(8):567-70
Impact factor: 2.265; Q3

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7. Morphine treatment for neonatal abstinence syndrome: huge dosing variability underscores the need for a better clinical study design
Mian P, Tibboel D, Wildschut ED, van den Anker JN, Allegaert K

Introduction: At present, morphine is the most commonly used first-line therapy to treat Neonatal Abstinence Syndrome (NAS). Unfortunately, there is still lack of evidence and consensus to guide pharmacologic therapy for NAS. In this review, we provide an overview on dosing regimens of morphine currently reported to treat NAS,

with the aim to stimulate discussion on the need for a standardized dosing through better study design.
Evidence acquisition: A search strategy was performed in PubMed to identify studies that provide a dosing regimen used, or advised by a review or guideline for morphine to treat NAS. In addition, dosing regimens from labels and formularies were collected.
Evidence synthesis: On 138 articles identified, 33 were retained after reading the full-text. In addition, 10 articles were included based on reference check. Extensive variability was observed for dosing advice, threshold in the initiating phase, dosing advice and maximum dose in the escalating phase. The same applies for dosing advice and detail during weaning, dosing interval and stabilization phase.
Conclusions: This review shows a large variability in dosing regimens of morphine used to treat NAS. This is likely a reflection of the heterogeneous populations included in NAS studies, the lack of standardization in assessment tools and study outcomes. We suggest that the development and validation of a core outcome set, subsequently applied in pragmatic point-of-care clinical trials or specific subgroups (e.g. iatrogenic postnatal NAS) are useful approaches to improve the current setting.

Gepubliceerd: Minerva Pediatr 2019 Jun;71(3):263-86
Impact factor: 0.832; Q4

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8. Population Pharmacokinetic Modeling of Acetaminophen and Metabolites in Children After Cardiac Surgery With Cardiopulmonary Bypass
Mian P, Valkenburg AJ, Allegaert K, Koch BCP, Breatnach CV, Knibbe CAJ, Tibboel D, Krekels EHJ

Children undergoing cardiac surgery often receive acetaminophen (paracetamol) as part of their postoperative pain treatment. To date, there is no information on the pharmacokinetics (PK) of acetaminophen in this special population, even though differences, as a result of altered hemodynamics and/or use of cardiopulmonary bypass, may be anticipated. Therefore, the aim of this study was to investigate the PK of intravenous acetaminophen in children after cardiac surgery with cardiopulmonary bypass. In the study, both children with and without Down syndrome were included. A population PK analysis, using NONMEM 7.2, was performed based on 161 concentrations of acetaminophen, acetaminophen sulfate, acetaminophen glucuronide, and oxidative metabolites from 17 children with Down syndrome and 13 children without Down syndrome of a previously published study (median age, 177 days [range, 92-944], body weight, 6.1 kg [4.0-12.9]). All children received 3 intravenous acetaminophen doses of 7.5 mg/kg (<10 kg) or 15 mg/kg (>/=10 kg) at 8-hour intervals after cardiac surgery. For acetaminophen and its metabolites, 1-compartment models were identified. Clearance of acetaminophen and metabolites increased linearly with body weight. Acetaminophen clearance in a typical child of 6.1 kg is 0.96 L/h and volume of distribution 7.96 L. Down syndrome did not statistically significantly impact any of the PK parameters for acetaminophen, nor did any other remaining covariate. When comparing the PK parameters of acetaminophen in children after cardiac surgery with cardiopulmonary bypass with those from children of the same age following noncardiac surgery reported in the literature, clearance of acetaminophen was lower and volume of distribution higher.

Gepubliceerd: J Clin Pharmacol 2019 Jun;59(6):847-55
Impact factor: 2.915; Q2

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9. Population pharmacokinetic modelling of intravenous paracetamol in fit older people displays extensive unexplained variability
Mian P, van Esdonk MJ, Olkkola KT, de Winter BCM, Liukas A, Spriet I, Tibboel D, Petrovic M, Koch BCP, Allegaert K

Aims: Paracetamol is the analgesic most used by older people. The physiological changes occurring with ageing influence the pharmacokinetics (PK) of paracetamol and its variability. We performed a population PK-analysis to describe the PK of intravenous (IV) paracetamol in fit older people. Simulations were performed to illustrate target attainment and variability of paracetamol exposure following current dosing regimens (1000 mg every 6 h, every 8 h) using steady-state concentration (Css-mean) of 10 mg l(-1) as target for effective analgesia.
Methods: A population PK-analysis, using NONMEM 7.2, was performed based on 601 concentrations of paracetamol from 30 fit older people (median age 77.3 years, range [61.8-88.5], body weight 79 kg [60-107]). All had received an IV paracetamol dose of 1000 mg (over 15 min) after elective knee surgery.
Results: A two-compartment PK-model best described the data. Volume of distribution of paracetamol increased exponentially with body weight. Clearance was not influenced by any covariate. Simulations of the standardized dosing regimens resulted in a Css of 9.2 mg l(-1) and 7.2 mg l(-1), for every 6 h and every 8 h respectively. Variability in paracetamol PK resulted in Css above 5.4 and 4.1 mg l(-1), respectively, in 90% of the population and above 15.5 and 11.7, respectively, in 10% at these dosing regimens.
Conclusions: The target concentration was achieved in the average patient with 1000 mg every 6 h, while every 8 h resulted in underdosing for the majority of the population. Furthermore, due to a large (unexplained) interindividual variability in paracetamol PK a relevant proportion of the fit older people remained either under- or over exposed.

Gepubliceerd: Br J Clin Pharmacol 2019 Jan;85(1):126-35
Impact factor: 3.867; Q1

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10. The effect of a structured medication review on quality of life in Parkinson's disease: The study protocol
Oonk NGM, Movig KLL, Munster EM, Koehorst-Ter Huurne K, van der Palen J, Dorresteijn LDA
Background: Treatment of Parkinson's disease (PD) is symptomatic and frequently consists of complicated medication regimes. This negatively influences therapy adherence, resulting in lower benefit of treatment, drug related problems and decreased quality of life (QoL). A potential effective intervention strategy is a structured medication review, executed by community pharmacists. However, little is known about the effects on clinical endpoints like QoL, as well as on feasibility and cost-effectiveness in PD patients. Objectives: To assess the effect of a structured medication review on QoL in PD patients. Secondary objectives are measurements of physical disability, activities in daily life, non-motor symptoms, health state, personal

carers' QoL and cost-effectiveness. Furthermore, a better insight in the process of performing medication reviews will be obtained from the perspective of community pharmacists.
Methods: In this multicenter randomized controlled trial we aim to enroll 200 PD patients from the outpatient clinic of three Dutch hospitals. Community pharmacists will perform a structured medication review in half of the assigned patients; the other half will receive usual care. Data obtained by use of six validated questionnaires will be collected at baseline and after 3 and 6 months of follow-up. Semi-structured interviews with community pharmacists will be conducted till data saturation has been reached.
Discussion: This trial targets a high-risk patient group for whom optimizing therapy by a structured medication review might be of added value. If effectiveness is proven, this could further promote the implementation of pharmaceutical care in a primary care setting.

Gepubliceerd: Contemp Clin Trials Commun 2019 Mar;13:100308
Impact factor: 0; nvt

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11. Pregnancy affects the pharmacokinetics of sildenafil and its metabolite in the rabbit
Russo FM, Mian P, Krekels EH, van Calsteren K, Tibboel D, Deprest J, Allegaert K

1. There is growing interest in the use of sildenafil during pregnancy for various maternal and fetal conditions. This study aims to investigate the effect of pregnancy on the maternal pharmacokinetics (PK) of sildenafil and its main metabolite desmethylsildenafil in rabbits. Using NONMEM, population PK modeling was performed based on plasma samples from 31 rabbits of whom 15 were pregnant and 16 were not. All received a single subcutaneous sildenafil dose of 10 mg/kg. One sample was obtained per rabbit at either 30, 60, 120, 360, 720 or 1320 min after sildenafil administration.
2. A two- and one-compartment PK-model best described the data for sildenafil and desmethylsildenafil, respectively. Compared to non-pregnant rabbits, the central and peripheral volume of distribution and inter-compartmental clearance of sildenafil were lower in pregnant rabbits [32.1 versus 12.2 L, 110 versus 44.4 L and 25.5 versus 12.1 L/h; all $p < 0.05$]. The formation clearance from sildenafil to desmethylsildenafil was also reduced during pregnancy [13.3 versus 7.8 L/h; $p < 0.05$].
3. In contrast, the elimination clearance of desmethylsildenafil, was higher in pregnancy [73.5 versus 116. 9; $p < 0.05$]. In rabbits, pregnancy impacts PK parameters of sildenafil and its metabolite, leading to an increased peak concentration and 24 h exposure for sildenafil and a decreased 24 h exposure for desmethylsildenafil.

Gepubliceerd: Xenobiotica 2019 Jan;49(1):98-105
Impact factor: 1.902; Q3

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12. Pharmacotherapy within a learning healthcare system: rationale for the Dutch Santeon Farmadatabase

van de Garde EMW, Plouvier BC, Fleuren HWHA, Haak EAF, Movig KLL, Deenen MJ, van HM

Objectives: The increasing number of available, often expensive, medicines asks for continuous assessment of rational prescribing. We aimed to develop a simple and robust data infrastructure in order to monitor hospital medicine utilisation in real time.
Methods: Within a collaboration (Santeon) of large teaching hospitals in the Netherlands, we set up a process for extraction, transformation, anonymisation and load of individual medicine prescription data and major clinical outcomes from different hospital information systems into a central database. Quarterly reports were constructed to monitor and validate the quality of the uploaded data.
Results: A central database has been developed that includes data from all patients from 2010 onwards and is refreshed on a weekly basis by an automated process. Beginning in 2017, the database holds data from almost 800 000 patients with prescriptions. All hospitals provide at least 18 mandatory data items per patient. Provided data include, among others, individual prescriptions, diagnosis data, and hospitalisation and survival data. The database is currently used to benchmark the level of biosimilar prescribing and to assess the impact of novel systemic treatments on survival rates in metastatic cancers.
Conclusion: We showed that it is feasible for a group of hospitals to construct their own database that can serve as a tool to benchmark the positioning of medicines and to start with monitoring their impact on clinical outcomes.

Gepubliceerd: Eur J Hosp Pharm 2019 Jan;26(1):46-50
Impact factor: 0.717; Q4

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13. Optimising pharmacotherapy in older cancer patients with polypharmacy
Vrijkorte E, de Vries J, Schaafsma R, Wymenga M, Oude Munnink T

Objective: Polypharmacy is frequent among older cancer patients and increases the risk of potential drug-related problems (DRPs). DRPs are associated with adverse drug events, drug-drug interactions and hospitalisations. Since no standardised polypharmacy assessment methods for oncology patients exist, we aimed to develop one that can be integrated into routine care.
Methods: Based on the Systematic Tool to Reduce Inappropriate Prescribing (STRIP), we developed OncoSTRIP, which includes a polypharmacy anamnesis, a concise geriatric assessment, a polypharmacy analysis taking life expectancy into account and an optimised treatment plan. Patients >/=65 years with >/=5 chronic drugs visiting our outpatient oncology clinic were eligible for the polypharmacy assessment.
Results: OncoSTRIP was integrated into routine care of our older cancer patients. In 47 of 60 patients (78%), potential DRPs (n = 101) were found. In total, 85 optimisations were recommended, with an acceptance rate of 41%. It was possible to reduce the number of potential DRPs by 41% and the number of patients with at least one potential DRP by 30%. Mean time spent per patient was 71 min.
Conclusions: Polypharmacy assessment of older cancer patients identifies many pharmacotherapeutic optimisations. With OncoSTRIP, polypharmacy assessments can be integrated into routine care.

Gepubliceerd: Eur J Cancer Care (Engl) 2019 Nov 6;e13185
Impact factor: 2.421; Q1

Totale impact factor: 95.985
Gemiddelde impact factor: 7.383

Aantal artikelen 1e, 2e of laatste auteur: 9
Totale impact factor: 20.481
Gemiddelde impact factor: 2.276

Klinische psychologie

1. Clinical and genetic characteristics of late-onset Huntington's disease
Oosterloo M, Bijlsma EK, van Kuijk SM, Minkels F, de Die-Smulders CE, REGISTRY Investigators of the European Huntington's Disease Network, includes van Hout M and van Vugt JPP

Background: The frequency of late-onset Huntington's disease (>59 years) is assumed to be low and the clinical course milder. However, previous literature on late-onset disease is scarce and inconclusive. OBJECTIVE: Our aim is to study clinical characteristics of late-onset compared to common-onset HD patients in a large cohort of HD patients from the Registry database.
Methods: Participants with late- and common-onset (30-50 years)were compared for first clinical symptoms, disease progression, CAG repeat size and family history. Participants with a missing CAG repeat size, a repeat size of </=35 or a UHDRS motor score of </=5 were excluded.
Results: Of 6007 eligible participants, 687 had late-onset (11.4%) and 3216 (53.5%) common-onset HD. Late-onset (n=577) had significantly more gait and balance problems as first symptom compared to common-onset (n=2408) (P<.001). Overall motor and cognitive performance (P<.001) were worse, however only disease motor progression was slower (coefficient, -0.58; SE 0.16; P<.001) compared to the common-onset group. Repeat size was significantly lower in the late-onset (n=40.8; SD 1.6) compared to common-onset (n=44.4; SD 2.8) (P<.001). Fewer late-onset patients (n=451) had a positive family history compared to common-onset (n=2940) (P<.001).
Conclusions: Late-onset patients present more frequently with gait and balance problems as first symptom, and disease progression is not milder compared to common-onset HD patients apart from motor progression. The family history is likely to be negative, which might make diagnosing HD more difficult in this population. However, the balance and gait problems might be helpful in diagnosing HD in elderly patients.

Gepubliceerd: Parkinsonism Relat Disord 2019;61:101-5
Impact factor: 4.360; Q1

Totale impact factor: 4.360
Gemiddelde impact factor: 4.360

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

Longgeneeskunde

1. Time-based capnography detects ineffective triggering in mechanically ventilated children
Blokpoel RGT, Koopman AA, van Dijk J, de Jongh FHC, Burgerhof JGM, Kneyber MCJ

Gepubliceerd: Crit Care 2019 Sep 4;23(1):299
Impact factor: 6.959; Q1

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2. Comparison of Veterans Affairs, Mayo, Brock classification models and radiologist diagnosis for classifying the malignancy of pulmonary nodules in Chinese clinical population
Cui X, Heuvelmans MA, Han D, Zhao Y, Fan S, Zheng S, Sidorenkov G, Groen HJM, Dorrius MD, Oudkerk M, de Bock GH, Vliegenthart R, Ye Z

Background: Several classification models based on Western population have been developed to help clinicians to classify the malignancy probability of pulmonary nodules. However, the diagnostic performance of these Western models in Chinese population is unknown. This paper aimed to compare the diagnostic performance of radiologist evaluation of malignancy probability and three classification models (Mayo Clinic, Veterans Affairs, and Brock University) in Chinese clinical pulmonology patients.
Methods: This single-center retrospective study included clinical patients from Tianjin Medical University Cancer Institute and Hospital with new, CT-detected pulmonary nodules in 2013. Patients with a nodule with diameter of 4-25 mm, and histological diagnosis or 2-year follow-up were included. Analysis of area under the receiver operating characteristic curve (AUC), decision curve analysis (DCA) and threshold of decision analysis was used to evaluate the diagnostic performance of radiologist diagnosis and the three classification models, with histological diagnosis or 2-year follow-up as the reference.
Results: In total, 277 patients (286 nodules) were included. Two hundred and seven of 286 nodules (72.4%) in 203 patients were malignant. AUC of the Mayo model (0.77; 95% CI: 0.72-0.82) and Brock model (0.77; 95% CI: 0.72-0.82) were similar to radiologist diagnosis (0.78; 95% CI: 0.73-0.83; P=0.68, P=0.71, respectively). The diagnostic performance of the VA model (AUC: 0.66) was significantly lower than that of radiologist diagnosis (P=0.003). A three-class classifying threshold analysis and DCA showed that the radiologist evaluation had higher discriminatory power for malignancy than the three classification models.
Conclusions: In a cohort of Chinese clinical pulmonology patients, radiologist evaluation of lung nodule malignancy probability demonstrated higher diagnostic performance than Mayo, Brock, and VA classification models. To optimize nodule diagnosis and management, a new model with more radiological characteristics could be valuable.

Gepubliceerd: Transl Lung Cancer Res 2019 Oct;8(5):605-13
Impact factor: 4.806; Q1

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3. Doxapram Treatment and Diaphragmatic Activity in Preterm Infants
de Waal CG, Hutten GJ, Kraaijenga JV, de Jongh FH, van Kaam AH

Background: Doxapram is a treatment option for severe apnea of prematurity (AOP). However, the effect of doxapram on the diaphragm, the main respiratory muscle, is not known. OBJECTIVES: To investigate the effect of doxapram on diaphragmatic activity measured with transcutaneous electromyography of the diaphragm (dEMG).
Methods: A pilot study was conducted in a tertiary neonatal intensive care unit. Diaphragmatic activity was measured from 30 min before up to 3 h after the start of doxapram treatment. dEMG parameters were compared to baseline (5 min before doxapram treatment) and at 15, 60, 120 and 180 min after the start of doxapram infusion.
Results: Eleven preterm infants were included with a mean gestational age of 25.5 +/- 1.2 weeks and birth weight of 831 +/- 129 g. The amplitudedEMG, peakdEMG and tonicdEMG values did not change in the 3 h after the start of doxapram infusion compared to baseline. Clinically, the number of apnea episodes in the 24 h after doxapram treatment decreased significantly.
Conclusion: Doxapram infusion does not alter diaphragmatic activity measured with transcutaneous dEMG in preterm infants with AOP, indicating that its working mechanism is primarily on respiratory drive and not on respiratory muscle activity.

Gepubliceerd: Neonatology 2019;115(1):85-8
Impact factor: 2.554; Q1

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4. Patient-ventilator asynchrony in preterm infants on nasal intermittent positive pressure ventilation
de Waal CG, van Leuteren RW, de Jongh FH, van Kaam AH, Hutten GJ

Objective: To describe the incidence of patient-ventilator asynchrony and different types of asynchrony in preterm infants treated with non-synchronised nasal intermittent positive pressure ventilation (nIPPV).
Design: An observational study was conducted including preterm infants born with a gestational age (GA) less than 32 weeks treated with non-synchronised nIPPV. During 1 hour, spontaneous breathing was measured with transcutaneous electromyography of the diaphragm simultaneous with ventilator inflations. An asynchrony index (AI), a percentage of asynchronous breaths, was calculated and the incidence of different types of inspiratory and expiratory asynchrony were reported.
Results: Twenty-one preterm infants with a mean GA of 26.0+/-1.2 weeks were included in the study. The mean inspiratory AI was 68.3%+/-4.7% and the mean expiratory AI was 67.1%+/-7.3%. Out of 5044 comparisons of spontaneous inspirations and mechanical inflations, 45.3% of the mechanical inflations occurred late, 23.3% of the mechanical inflations were early and 31.4% of the mechanical inflation were synchronous. 40.3% of 5127 expiratory comparisons showed an early termination of ventilator inflations, 26.7% of the mechanical inflations terminated late and 33.0% mechanical inflations terminated in synchrony with a spontaneous expiration. In addition, 1380 spontaneous breaths were unsupported and 611 extra mechanical inflations were delivered.

Conclusion: Non-synchronised nIPPV results in high patient-ventilator asynchrony in preterm infants during both the inspiratory and expiratory phase of the breathing cycle. New synchronisation techniques are urgently needed and should address both inspiratory and expiratory asynchrony.

Gepubliceerd: Arch Dis Child Fetal Neonatal Ed 2019;104(3):F280-F284
Impact factor: 3.158; Q1

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5. Methods of computed tomography screening and management of lung cancer in Tianjin: design of a population-based cohort study
Du Y, Zhao Y, Sidorenkov G, de Bock GH, Cui X, Huang Y, Dorrius MD, Rook M, Groen HJM, Heuvelmans MA, Vliegenthart R, Chen K, Xie X, Liu S, Oudkerk M, Ye Z

Objective: European lung cancer screening studies using computed tomography (CT) have shown that a management protocol based on measuring lung nodule volume and volume doubling time (VDT) is more specific for early lung cancer detection than a diameter-based protocol. However, whether this also applies to a Chinese population is unclear. The aim of this study is to compare the diagnostic performance of a volume-based protocol with a diameter-based protocol for lung cancer detection and optimize the nodule management criteria for a Chinese population.
Methods: This study has a population-based, prospective cohort design and includes 4000 participants from the Hexi district of Tianjin, China. Participants will undergo low-dose chest CT at baseline and after 1 year. Initially, detected lung nodules will be evaluated for diameter and managed according to a routine diameter-based protocol (Clinical Practice Guideline in Oncology for Lung Cancer Screening, Version 2.2018). Subsequently, lung nodules will be evaluated for volume and management will be simulated according to a volume-based protocol and VDT (a European lung nodule management protocol). Participants will be followed up for 4 years to evaluate lung cancer incidence and mortality. The primary outcome is the diagnostic performance of the European volume-based protocol compared to diameter-based management regarding lung nodules detected using low-dose CT.
Results: The diagnostic performance of volume- and diameter-based management for lung nodules in a Chinese population will be estimated and compared.
Conclusions: Through the study, we expect to improve the management of lung nodules and early detection of lung cancer in Chinese populations.

Gepubliceerd: Cancer Biol Med 2019 Feb;16(1):181-8
Impact factor: 4.467; Q1

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6. Validation of the oxygen desaturation index in the diagnostic workup of obstructive sleep apnea
Fabius TM, Benistant JR, Bekkedam L, van der Palen J, de Jongh FHC, Eijsvogel MMM

Introduction: Obstructive sleep apnea (OSA) is common, and diagnosis requires expensive and laborious testing to assess the apnea hypopnea index (AHI). We performed an analysis to explore the relationship between the oxygen desaturation

index (ODI) as measured with pulse oximetry and the AHI in our large portable monitoring (PM) database to find an optimal cutoff value for the ODI in order to be able to exclude AHI >/= 5 on PM.
Methods: Three thousand four hundred thirteen PM recordings were randomly divided into a training set (N = 2281) and a test set (N = 1132). The optimal cutoff for the ODI to exclude an AHI >/= 5 on PM was determined in the training set and subsequently validated in the test set.
Results: Area under the curve of the ODI to exclude an AHI >/= 5 on PM was 0.997 in the training set and 0.996 in the test set. In the training set, the optimal cutoff to predict an AHI < 5 was an ODI < 5. Using this cutoff in the test set provided a sensitivity of 97.7%, a specificity of 97.0%, a positive predictive value of 99.2%, and a negative predictive value of 91.4%.
Conclusion: An ODI < 5 predicts an AHI < 5 with high sensitivity and specificity when measured simultaneously using the same oximeter during PM recording.

Gepubliceerd: Sleep Breath 2019;23(1):57-63
Impact factor: 2.326; Q3

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7. Reply from the authors: Additional factors to consider with regard to condensation in bench studies
Flink RC, van Kaam AH, de Jongh FH

Gepubliceerd: Acta Paediatr 2019;108(2):380
Impact factor: 2.265; Q2

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8. An Update on the European Lung Cancer Screening Trials and Comparison of Lung Cancer Screening Recommendations in Europe
Han D, Heuvelmans MA, Vliegenthart R, Rook M, Dorrius MD, Oudkerk M

While lung cancer screening has been implemented in the United States, it is still under consideration in Europe. So far, lung cancer screening trials in Europe were not able to replicate the results of the National Lung Screening Trial, but they do show a stage shift in the lung cancers that were detected. While eagerly awaiting the final result of the only lung cancer screening trial with sufficient statistical power, the NELSON trial, a number of European countries and medical societies have published recommendations for lung cancer screening using computed tomography. However, there is still a debate with regard to the design of future lung cancer screening programs in Europe. This review summarizes the latest evidence of European lung cancer screening trials and gives an overview of the essence of recommendations from the different European medical societies and countries.

Gepubliceerd: J Thorac Imaging 2019;34(1):65-71
Impact factor: 2.078; Q3

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9. Screening for Early Lung Cancer, Chronic Obstructive Pulmonary Disease, and Cardiovascular Disease (the Big-3) Using Low-dose Chest Computed Tomography: Current Evidence and Technical Considerations

Heuvelmans MA, Vonder M, Rook M, Groen HJM, de Bock GH, Xie X, Ijzerman MJ, Vliegenthart R, Oudkerk M

Lung cancer, chronic obstructive pulmonary disease, and cardiovascular disease are highly prevalent in the general population and expected to cause most deaths by 2050. For these "Big-3," treatment might cure, delay, or stop the progression of disease at a very early stage. Lung nodule growth rate (a biomarker for lung cancer), emphysema/air trapping (a biomarker for chronic obstructive pulmonary disease), and coronary artery calcification (a biomarker for cardiovascular disease) are imaging biomarkers of early stages of the Big-3 that can be acquired with low-dose computed tomography (CT). We hypothesize that a (combined) low-dose CT examination for detection of all 3 diseases may significantly improve the cost-effectiveness of screening in the future. We review the current evidence of the imaging biomarkers for the detection of the Big-3 diseases and present the potential health economic potential of Big-3 screening. Furthermore, we review the low-dose CT protocols to acquire these biomarkers and describe the technical considerations when combining the CT protocols for the different biomarkers.

Gepubliceerd: J Thorac Imaging 2019 May;34(3):160-9
Impact factor: 2.078; Q3

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10. Exacerbation action plans for patients with COPD and comorbidities: a randomised controlled trial
Lenferink A, van der Palen J, van der Valk PDLP, Cafarella P, van Veen A, Quinn S, Groothuis-Oudshoorn CGM, Burt MG, Young M, Frith PA, Effing TW

This international randomised controlled trial evaluated whether COPD patients with comorbidities, trained in using patient-tailored multidisease exacerbation action plans, had fewer COPD exacerbation days than usual care (UC).COPD patients (Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification II-IV) with >/=1 comorbidity (ischaemic heart disease, heart failure, diabetes, anxiety, depression) were randomised to a patient-tailored self-management intervention (n=102) or UC (n=99). Daily symptom diaries were completed for 12 months. The primary outcome "COPD exacerbation days per patient per year" was assessed using intention-to-treat analyses.No significant difference was observed in the number of COPD exacerbation days per patient per year (self-management: median 9.6 (interquartile range (IQR) 0.7-31.1); UC: median 15.6 (IQR 3.0-40.3); incidence rate ratio (IRR) 0.87 (95% CI 0.54; 1.39); p=0.546). There was a significantly shorter duration per COPD exacerbation for self-management (self-management: median 8.1 (IQR 4.8-10.1) days; UC: median 9.5 (IQR 7.0-15.1) days; p=0.021), with no between-group differences in the total number of respiratory hospitalisations (IRR 0.76 (95% CI 0.42; 1.35); p=0.348), but a lower probability of >/=1 for respiratory-related hospitalisation compared to UC (relative risk 0.55 (95% CI 0.35; 0.87); p=0.008). No between-group differences were observed in all-cause hospitalisations (IRR 1.07 (95% CI 0.66; 1.72)) or mortality (self-management: n=4 (3.9%); UC: n=7 (7.1%); relative risk 0.55 (95% CI 0.17; 1.84)).Patient-tailored exacerbation action plans for COPD patients with comorbidities did not significantly reduce exacerbation days, but reduced the duration per COPD exacerbation and the risk of having at least one respiratory-related hospitalisation during follow-up, without excess all-cause mortality.

Gepubliceerd: Eur Respir J 2019 Nov;54(5):1802134
Impact factor: 11.807; Q1

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11. Impact of atrial septal defect closure on diffusing capacity for nitric oxide and carbon monoxide
Nassif M, van Steenwijk RP, van der Lee I, Sterk PJ, de Jongh FHC, Hogenhout JM, Tijssen JGP, Mulder BJM, de Winter RJ

Atrial septal defects are characterised by a low D LNO /D LCOc ratio in diffusion testing. Successful percutaneous closure shows an increase in D LNO /D LCOc ratio and vital capacity through correction of a hyperdynamic pulmonary circulation.

Gepubliceerd: ERJ Open Res 2019 Apr;5(2): 00260-2018
Impact factor: 0; nvt

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12. A 37-Year-Old Woman With Recurrent Hemoptysis
Schoonbeek RC, Wagenaar M, Baidoshvili A, van Veen IHPA

Case presentation: A 37-year-old woman presented with a 2-month history of recurrent hemoptysis and coughing. Her symptoms started 2 months after the delivery of her third child. In total, she endured four episodes of hemoptysis. All pregnancies were induced by intracytoplasmic sperm injections. She lacked a pulmonary or smoking history and had no history of foreign body aspiration or intubation. There was no dyspnea, dysphagia, fever, or chest pain, and the patient did not complain of purulent sputum. She currently did not use medication and was generally in good health.

Gepubliceerd: Chest 2019 Oct;156(4):e81-e84
Impact factor: 9.657; Q1

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13. Processing transcutaneous electromyography measurements of respiratory muscles, a review of analysis techniques
van Leuteren RW, Hutten GJ, de Waal CG, Dixon P, van Kaam AH, de Jongh FH

Transcutaneous electromyography (tc-EMG) has been used to measure the electrical activity of respiratory muscles during inspiration in various studies. Processing the raw tc-EMG signal of these inspiratory muscles has shown to be difficult as baseline noise, cardiac interference, cross-talk and motion artefacts can influence the signal quality. In this review we will discuss the most important sources of signal noise in tc-EMG of respiratory muscles and the various techniques described to suppress or reduce this signal noise. Furthermore, we will elaborate on the options available to develop or improve an algorithm that can be used to guide the approach for analysis of tc-EMG signals of inspiratory muscles in future research.

Gepubliceerd: J Electromyogr Kinesiol 2019 Oct;48:176-86
Impact factor: 1.753; Q2

14. Persisting new nodules in incidence rounds of the NELSON CT lung cancer screening study
Walter JE, Heuvelmans MA, Ten Haaf K, Vliegenthart R, van der Aalst CM, Yousaf-Khan U, van Ooijen PMA, Nackaerts K, Groen HJM, de Bock GH, de Koning HJ, Oudkerk M

Background: The US guidelines recommend low-dose CT (LDCT) lung cancer screening for high-risk individuals. New solid nodules after baseline screening are common and have a high lung cancer probability. Currently, no evidence exists concerning the risk stratification of non-resolving new solid nodules at first LDCT screening after initial detection.
Methods: In the Dutch-Belgian Randomized Lung Cancer Screening (NELSON) trial, 7295 participants underwent the second and 6922 participants the third screening round. We included participants with solid nodules that were registered as new or <15 mm(3) (study detection limit) at previous screens and received additional screening after initial detection, thereby excluding high-risk nodules according to the NELSON management protocol (nodules >/=500 mm(3)).
Results: Overall, 680 participants with 1020 low-risk and intermediate-risk new solid nodules were included. A total of 562 (55%) new solid nodules were resolving, leaving 356 (52%) participants with a non-resolving new solid nodule, of whom 25 (7%) were diagnosed with lung cancer. At first screening after initial detection, volume doubling time (VDT), volume, and VDT combined with a predefined >/=200 mm(3) volume cut-off had high discrimination for lung cancer (VDT, area under the curve (AUC): 0.913; volume, AUC: 0.875; VDT and >/=200 mm(3) combination, AUC: 0.939). Classifying a new solid nodule with either </=590 days VDT or >/=200 mm(3) volume positive provided 100% sensitivity, 84% specificity and 27% positive predictive value for lung cancer.
Conclusions: More than half of new low-risk and intermediate-risk solid nodules in LDCT lung cancer screening resolve. At follow-up, growth assessment potentially combined with a volume limit can be used for risk stratification.
Trial registration number: ISRCTN63545820; pre-results.

Gepubliceerd: Thorax 2019;74(3):247-53
Impact factor: 10.307; Q1

Totale impact factor: 64.215
Gemiddelde impact factor: 4.587

Aantal artikelen 1e, 2e of laatste auteur: 9
Totale impact factor: 47.077
Gemiddelde impact factor: 5.231

MDL

1. The Impact of Revascularisation on Quality of Life in Chronic Mesenteric Ischemia
Blauw JTM, Pastoors HAM, Brusse-Keizer M, Beuk RJ, Kolkman JJ, Geelkerken RH, For The Dutch Mesenteric Ischemia Study Group
Background: Chronic mesenteric ischemia (CMI) is characterized by long-standing abdominal symptoms due to insufficient mesenteric circulation. Data on the effect of revascularisation on quality of life (QoL) for CMI are scarce. This study is the first to evaluate the impact of revascularisation on quality of life.
Methods: Seventy-nine patients with CMI or acute-on-chronic mesenteric ischemia (AoCMI) underwent an intervention of one or more mesenteric arteries between January 2010 and July 2012. QoL before and after intervention was measured with the EuroQol-5D. Preintervention questionnaires were of standard care. Postintervention data were obtained by resending a questionnaire to the patients between February and May 2013. To investigate the clinical relevance of our findings, the minimal clinically important difference (MCID) was used. Since there is no established MCID for CMI, we used the literature reference MCID of inflammatory bowel syndrome (IBS) of 0.074.
Results: Fifty-five (69.6%) of 79 patients returned their questionnaire and 23 (29.1%) were completely filled out. There was a significant increase of the median EQ-index score from 0.70 to 0.81 (p=0.02) and a significant reduction of symptoms in the domains usual activities (34.4%) and pain/discomfort (32.3%). There was a significant improvement of 17% in overall current health condition (VAS) (p=0.001). The MCID between baseline and postoperative EQ-5D index score was 0.162, indicating a clinically relevant improvement of quality of life after revascularisation.
Conclusion: Quality of life of CMI patients is improved after mesenteric artery revascularisation.

Gepubliceerd: Can J Gastroenterol Hepatol 2019;2019:7346013
Impact factor: 1.714; Q4

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2. A Case Report of a Young Adult With Progressive Bloody Diarrhea, Protein-Losing Enteropathy, and Extended Polyposis Coli
Borgerink MMH, Weersma RK, Visschedijk MC

Gepubliceerd: Gastroenterology 2019 Jan;156(1):e10-e11
Impact factor: 19.809; Q1

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3. Sucrose but Not Nitrate Ingestion Reduces Strenuous Cycling-induced Intestinal Injury
Jonvik KL, Lenaerts K, Smeets JS, Kolkman JJ, Loon LJV, Verdijk LB

Purpose: Strenuous exercise induces intestinal injury, which is likely related to splanchnic hypoperfusion and may be associated with gastrointestinal complaints commonly reported during certain exercise modalities. Increasing circulating nitric oxide (NO) levels or inducing postprandial hyperemia may improve splanchnic

perfusion, thereby attenuating intestinal injury during exercise. Therefore, we investigated the effects of both dietary nitrate ingestion and sucrose ingestion on splanchnic perfusion and intestinal injury induced by prolonged strenuous cycling.
Methods: In a randomized cross-over manner, 16 well-trained male athletes (age: 28+/-7 y; Wmax: 5.0+/-0.3 W.kg) cycled 60 min at 70% Wmax following acute ingestion of: sodium nitrate (NIT; 800 mg NO3), sucrose (SUC; 40 g) or a water placebo (PLA). Splanchnic perfusion was assessed by determining the gap between gastric and arterial pCO2 (gapg-apCO2) using gastric air tonometry. Plasma intestinal fatty-acid binding protein (I-FABP) concentrations, reflecting enterocyte damage, were assessed every 20 min during and up to 60 min of post-exercise recovery.
Results: The exercise protocol resulted in splanchnic hypoperfusion, as gapg-apCO2 levels increased during exercise (P<0.001), with no differences between treatments (P=0.47). Although plasma I-FABP concentrations increased during exercise and post-exercise recovery for all treatments (P<0.0001), the increase was different between treatments (P<0.0001). Post-hoc comparisons showed an attenuated increase in I-FABP in SUC vs PLA (P=0.020). In accordance, I-FABP area under the curve (AUC0-120) was significantly lower in SUC vs PLA (57,270+/-77,425 vs 114,907+/-91,527 pg.mL.120 min, P=0.002). No differences were observed between NIT and PLA (P=0.99).
Conclusion: Sucrose but not nitrate ingestion lowers intestinal injury evoked during prolonged strenuous cycling. These results suggest that sucrose ingestion, but not nitrate, prevents hypoperfusion-induced gastrointestinal damage during exercise and, as such, may help to lower exercise-related gastrointestinal complaints.

Gepubliceerd: Med Sci Sports Exerc 2019;51(3):436-44
Impact factor: 4.478; Q1

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4. Pancreatic cyst surveillance imposes low psychological burden
Overbeek KA, Kamps A, van Riet PA, Di Marco M, Zerboni G, van Hooft JE, Carrara S, Ricci C, Gonda TA, Schoon E, Polkowski M, Beyer G, Honkoop P, van der Waaij LA, Casadei R, Capurso G, Erler NS, Bruno MJ, Bleiker EMA, Cahen DL, PACYFIC study group, includes Venneman NG

Background/Objectives: For the currently recommended pancreatic cyst surveillance to be feasible, participant adherence is a prerequisite. Our objective was to evaluate the psychological burden of pancreatic cyst surveillance from a participant's perspective.
Methods: The present participant survey is part of an international cohort study (PACYFIC study, www.pacyfic.net), which prospectively records the outcome of surveillance of asymptomatic pancreatic cysts. Participants are invited to complete questionnaires before and during cyst surveillance.
Results: 109 participants, 31 enrolled before and 78 during surveillance (median time since cyst diagnosis 16.5 (IQR 36) months), returned a total of 179 questionnaires. The majority indicated that surveillance reduces concerns of developing pancreatic cancer (82%), gives a sense of certainty (81%) and is a good method to detect cancer (91%). Participants already undergoing surveillance reported more negative aspects than those still to commence, like sleeping worse (30% vs 13%, P=0.035), postponing plans (32% vs 13%, P=0.031), and finding the follow-up burdensome (33% vs 13%, P=0.044). Overall, the vast majority (94%) deemed advantages to

outweigh disadvantages. Anxiety and depression scores were low (median Hospital Anxiety and Depression Scale 4 for anxiety (IQR 6), 2 for depression (IQR 5)).
Conclusion: The psychological burden of pancreatic cyst surveillance is low. Therefore, participant adherence is expected to be high and annual surveillance seems feasible.

Gepubliceerd: Pancreatology 2019 Sep 5;19(8):1061-6
Impact factor: 3.241; Q2

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5. The Oxysterol Synthesising Enzyme CH25H Contributes to the Development of Intestinal Fibrosis
Raselli T, Wyss A, Gonzalez Alvarado MN, Weder B, Mamie C, Spalinger MR, Van Haaften WT, Dijkstra G, Sailer AW, Imenez Silva PH, Wagner CA, Tosevski V, Leibl S, Scharl M, Rogler G, Hausmann M, Misselwitz B

Intestinal fibrosis and stenosis are common complications of Crohn's disease [CD], frequently requiring surgery. Anti-inflammatory strategies can only partially prevent fibrosis; hence, anti-fibrotic therapies remain an unmet clinical need. Oxysterols are oxidised cholesterol derivatives with important roles in various biological processes. The enzyme cholesterol 25-hydroxylase [CH25H] converts cholesterol to 25-hydroxycholesterol [25-HC], which modulates immune responses and oxidative stress. In human intestinal samples from CD patients, we found a strong correlation of CH25H mRNA expression with the expression of fibrosis markers. We demonstrate reduced intestinal fibrosis in mice deficient for the CH25H enzyme, using the sodium dextran sulphate [DSS]-induced chronic colitis model. Additionally, using a heterotopic transplantation model of intestinal fibrosis, we demonstrate reduced collagen deposition and lower concentrations of hydroxyproline in CH25H knockouts. In the heterotopic transplant model, CH25H was expressed in fibroblasts. Taken together, our findings indicate an involvement of oxysterol synthesis in the pathogenesis of intestinal fibrosis.

Gepubliceerd: J Crohns Colitis 2019 Sep 19;13(9):1186-200
Impact factor: 7.827; Q1

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6. The revised Atlanta criteria more accurately reflect severity of post-ERCP pancreatitis compared to the consensus criteria
Smeets X, Bouhouch N, Buxbaum J, Zhang H, Cho J, Verdonk RC, Romkens T, Venneman NG, Kats I, Vrolijk JM, Hemmink G, Otten A, Tan A, Elmunzer BJ, Cotton PB, Drenth J, van Geenen E

Background and objective: Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is the most prevalent complication after ERCP with an incidence of 3.5%. PEP severity is classified according to either the consensus criteria or the revised Atlanta criteria. In this international cohort study we investigated which classification is the strongest predictor of PEP-related mortality.
Methods: We reviewed 13,384 consecutive ERCPs performed between 2012 and 2017 in eight hospitals. We gathered data on all pancreatitis-related adverse events and compared the predictive capabilities of both classifications. Furthermore, we

investigated the correlation between the two classifications and identified reasons underlying length of stay.
Results: The total sample consisted of 387 patients. The revised Atlanta criteria have a higher sensitivity (100 vs. 55%), specificity (98 vs. 72%) and positive predictive value (58 vs. 5%). There is a significant difference ($p < 0.001$) between the two classifications. In 124 patients (32%), the length of stay was influenced by concomitant diseases.
Conclusion: The revised Atlanta classification is superior in predicting mortality and better reflects PEP severity. This has important implications for researchers, clinicians and patients. For the diagnosis of PEP pancreatitis, the consensus criteria remain the golden standard. However, the revised Atlanta criteria are preferable for defining PEP severity.

Gepubliceerd: United European Gastroenterol J 2019 May;7(4):557-64
Impact factor: 3.453; Q2

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7. The association between portal system vein diameters and outcomes in acute pancreatitis
Smeets XJNM, Litjens G, da Costa DW, Kievit W, van Santvoort HC, Besselink MGH, Fockens P, Bruno MJ, Kolkman JJ, Drenth JPH, Bollen TL, van Geenen EJM

Background/Objectives: Acute pancreatitis (AP) progresses to necrotizing pancreatitis in 15% of cases. An important pathophysiological mechanism in AP is third spacing of fluids, which leads to intravascular volume depletion. This results in a reduced splanchnic circulation and reduced venous return. Non-visualisation of the portal and splenic vein on early computed tomography (CT) scan, which might be the result of smaller vein diameter due to decreased venous flow, is associated with infected necrosis and mortality in AP. This observation led us to hypothesize that smaller diameters of portal system veins (portal, splenic and superior mesenteric) are associated with increased severity of AP.
Methods: We conducted a post-hoc analysis of data from two randomized controlled trials that included patients with predicted severe and mild AP. The primary endpoint was AP-related mortality. The secondary endpoints were (infected) necrotizing pancreatitis and (persistent) organ failure. We performed additional CT measurements of portal system vein diameters and calculated their prognostic value through univariate and multivariate Poisson regression.
Results: Multivariate regression showed a significant inverse association between splenic vein diameter and mortality (RR 0.75 (0.59-0.97)). Furthermore, there was a significant inverse association between splenic and superior mesenteric vein diameter and (infected) necrosis. Diameters of all veins were inversely associated with organ failure and persistent organ failure.
Conclusions: We observed an inverse relationship between portal system vein diameter and morbidity and an inverse relationship between splenic vein diameter and mortality in AP. Further research is needed to test whether these results can be implemented in predictive scoring systems.

Gepubliceerd: Pancreatology 2019;31(3):316-22
Impact factor: 3.241; Q2

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8. Pancreatic ductal adenocarcinoma and chronic pancreatitis may be diagnosed by exhaled-breath profiles: a multicenter pilot study
Uslu HI, Dolle AR, Dullemen HM, Aktas H, Kolkman JJ, Venneman NG

Background: The diagnosis of pancreatic adenocarcinoma and chronic pancreatitis often rely on expensive and invasive diagnostic approaches, which are not always discriminative since patients with chronic pancreatitis and pancreatic adenocarcinoma may present with similar symptoms. Volatile organic compounds (VOCs) in expired breath, could be used as a non-invasive diagnostic biological marker for detection of pancreatic pathology. Detection and discrimination of pancreatic pathology with an electronic nose has not yet been reported.
Purpose: The objective of this pilot study was to determine the diagnostic potential of an electronic nose to identify pancreatic adenocarcinoma and chronic pancreatitis by analyzing volatile organic compoundg (VOC) profiles in exhaled air. Patients and methods: In a multicenter study, the exhaled air of 56 chronic pancreatitis patients, 29 pancreatic adenocarcinoma patients, and 74 disease controls were analyzed using an electronic nose based on 3 metal oxide sensors (MOS). The measurements were evaluated utilizing an artificial neural network.
Results: VOC profiles of chronic pancreatitis patients could be discriminated from disease controls with an accuracy of 0.87 (AUC 0.95, sensitivity 80%, specificity 92%). Also, VOC profiles of patients with pancreatic adenocarcinoma differed from disease controls with an accuracy of 0.83 (AUC 0.87, sensitivity 83%, specificity 82%). Discrimination between chronic pancreatitis and pancreatic adenocarcinoma showed an accuracy of 0.75 (AUC 0.83, sensitivity 83%, specificity 71%).
Conclusion: An electronic nose may be a valuable diagnostic tool in diagnosis of pancreatic adenocarcinoma and chronic pancreatitis. The current study shows the potential of an electronic nose for discriminating between chronic pancreatitis, pancreatic adenocarcinoma and healthy controls. The results from this proof-of-concept study warrant external validation in larger cohorts.

Gepubliceerd: Clin Exp Gastroenterol 2019;12:385-90
Impact factor: 0; nvt

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9. Limited relevance and progression of histological alterations in the liver during thioguanine therapy in inflammatory bowel disease patients
van Asseldonk DP, Simsek M, de Boer NKH, Jharap B, Bloemena E, den Hartog G, Westerveld DB, Becx MC, Russel MG, Lissenberg-Witte BI, van Nieuwkerk CM, Mulder CJJ, Verheij J, van Bodegraven AA

Background: Thioguanine is associated with liver toxicity, especially nodular regenerative hyperplasia (NRH). We assessed if liver histology alters during long-term maintenance treatment with thioguanine in patients with inflammatory bowel disease (IBD).
Methods: Liver specimens of thioguanine treated IBD patients with at least two liver biopsies were revised by two independent liver pathologists, blinded to clinical characteristics. Alterations in histopathological findings between first and sequential liver specimen were evaluated and associated clinical data, including laboratory parameters and abdominal imaging reports, were collected.

Results: Twenty-five IBD patients underwent sequential liver biopsies prior to, at time of, or after cessation of thioguanine treatment. The median time between the first and second biopsy was 25 months (range: 14-54). Except for one normal liver specimen, any degree of irregularities including inflammation, steatosis, fibrosis and some vascular disturbances were observed in the biopsies. The rates of perisinusoidal fibrosis (91%), sinusoidal dilatation (68%) and nodularity (18%) were the same in the first and second liver biopsies. A trend towards statistical significance was observed for phlebosclerosis (36% of the first vs. 68% of the second biopsies, p = .092). Presence of histopathological liver abnormalities was not associated with clinical outcomes. Furthermore, two patients in this cohort had portal hypertension in presence of phlebosclerosis. In another two patients, nodularity of the liver resolved upon thioguanine withdrawal.
Conclusion: Vascular abnormalities of the liver were commonly observed in thioguanine treated IBD patients, although these were not progressive and remained of limited clinical relevance over time.

Gepubliceerd: Scand J Gastroenterol 2019 Jun;54(6):753-60
Impact factor: 2.152; Q4

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10. Increased Mortality Among Patients With vs Without Cirrhosis and Autoimmune Hepatitis
van den Brand FF, van der Veen KS, de Boer YS, van Gerven NM, Lissenberg-Witte BI, Beuers U, van Erpecum KJ, van Buuren HR, den Ouden JW, Brouwer JT, Vrolijk JM, Verdonk RC, van Hoek B, Koek GH, Drenth JPH, Guichelaar MMJ, Mulder CJJ, Bloemena E, van Nieuwkerk CMJ, Bouma G

Background & aims: There have been few reproducible studies of mortality in patients with autoimmune hepatitis (AIH) and its variants. We calculated mortality in a large national cohort of patients with AIH, with vs without cirrhosis, in the Netherlands.
Methods: We collected data from 449 patients with established AIH (77% female), from 6 academic and 10 non-academic hospitals in the Netherlands. We identified 29 patients with AIH and primary biliary cholangitis and 35 patients with AIH and primary sclerosing cholangitis (AIH-PSC). Mortality and liver transplantation data were assessed from August 1, 2006 through July 31, 2016. Standardized mortality ratios (SMR) were calculated using age-, sex-, and calendar year-matched mortality for the general Dutch population.
Results: During the 10-year follow-up period, 60 patients (13%) died (mean age, 71 years; range, 33-94 years). Twenty-six causes of death were liver related (43%), whereas the others could not be attributed to liver disease. Patients with AIH and cirrhosis had significantly higher mortality than the general population (SMR, 1.9; 95% CI, 1.2-3.4), whereas patients without cirrhosis did not (SMR, 1.2; 95% CI, 0.8-1.8). Patients with AIH-PSC had the largest increase in mortality, compared to the general population (SMR, 4.7; 95% CI, 1.5-14.6), of all groups analyzed. Mortality in patients with AIH and primary biliary cholangitis was not greater than the general population. Four or more relapses per decade or not achieving remission was associated with an increase in liver-related death or liver transplantation. Nine patients underwent liver transplantation; 2 died from non-liver related causes. Four of 9 patients on the waitlist for transplantation died before receiving a donated liver.

Conclusion: In an analysis of data from a large national cohort of patients with AIH, we found increased mortality of patients with cirrhosis, but not of patients without cirrhosis, compared to the general Dutch population. Survival was significantly reduced in patients with AIH and features of concurrent PSC.

Gepubliceerd: Clin Gastroenterol Hepatol 2019;4(3):199-207
Impact factor: 7.958; Q1

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11. Clinical management of chronic mesenteric ischemia
van Dijk LJ, van Noord D, de Vries AC, Kolkman JJ, Geelkerken RH, Verhagen HJ, Moelker A, Bruno MJ

This This Dutch Mesenteric Ischemia Study group consists of: Ron Balm, Academic Medical Center, Amsterdam Gert Jan de Borst, University Medical Center Utrecht, Utrecht Juliette T Blauw, Medisch Spectrum Twente, Enschede Marco J Bruno, Erasmus MC University Medical Center, Rotterdam Olaf J Bakker, St Antonius Hospital, Nieuwegein Louisa JD van Dijk, Erasmus MC University Medical Center, Rotterdam Hessel CJL Buscher, Gelre Hospitals, Apeldoorn Bram Fioole, Maasstad Hospital, Rotterdam Robert H Geelkerken, Medisch Spectrum Twente, Enschede Jaap F Hamming, Leiden University Medical Center, Leiden Jihan Harki, Erasmus MC University Medical Center, Rotterdam Daniel AF van den Heuvel, St Antonius Hospital, Nieuwegein Eline S van Hattum, University Medical Center Utrecht, Utrecht Jan Willem Hinnen, Jeroen Bosch Hospital, 's-Hertogenbosch Jeroen J Kolkman, Medisch Spectrum Twente, Enschede Maarten J van der Laan, University Medical Center Groningen, Groningen Kaatje Lenaerts, Maastricht University Medical Center, Maastricht Adriaan Moelker, Erasmus MC University Medical Center, Rotterdam Desiree van Noord, Franciscus Gasthuis & Vlietland, Rotterdam Maikel P Peppelenbosch, Erasmus MC University Medical Center, Rotterdam Andre S van Petersen, Bernhoven Hospital, Uden Pepijn Rijnja, Medisch Spectrum Twente, Enschede Peter J van der Schaar, St Antonius Hospital, Nieuwegein Luke G Terlouw, Erasmus MC University Medical Center, Rotterdam Hence JM Verhagen, Erasmus MC University Medical Center, Rotterdam Jean Paul PM de Vries, University Medical Center Groningen, Groningen Dammis Vroegindeweij, Maasstad Hospital, Rotterdam review provides an overview on the clinical management of chronic mesenteric ischemia (CMI). CMI is defined as insufficient blood supply to the gastrointestinal tract, most often caused by atherosclerotic stenosis of one or more mesenteric arteries. Patients classically present with postprandial abdominal pain and weight loss. However, patients may present with, atypically, symptoms such as abdominal discomfort, nausea, vomiting, diarrhea or constipation. Early consideration and diagnosis of CMI is important to timely treat, to improve quality of life and to prevent acute-on-chronic mesenteric ischemia. The diagnosis of CMI is based on the triad of clinical symptoms, radiological evaluation of the mesenteric vasculature and if available, functional assessment of mucosal ischemia. Multidisciplinary consensus on the diagnosis of CMI is of paramount importance to adequately select patients for treatment. Patients with a consensus diagnosis of single-vessel or multi-vessel atherosclerotic CMI are preferably treated with endovascular revascularization.

Gepubliceerd: United European Gastroenterol J 2019 Mar;7(2):179-88
Impact factor: 3.453; Q2

12. Validation of a score chart to predict the risk of chronic mesenteric ischemia and development of an updated score chart
van Dijk LJ, van Noord D, Geelkerken RH, Harki J, Berendsen SA, de Vries AC, Moelker A, Vergouwe Y, Verhagen HJ, Kolkman JJ, Bruno MJ

Background and objective: The objective of this article is to externally validate and update a recently published score chart for chronic mesenteric ischemia (CMI).
Methods: A multicenter prospective cohort analysis was conducted of 666 CMI-suspected patients referred to two Dutch specialized CMI centers. Multidisciplinary consultation resulted in expert-based consensus diagnosis after which CMI consensus patients were treated. A definitive diagnosis of CMI was established if successful treatment resulted in durable symptom relief. The absolute CMI risk was calculated and discriminative ability of the original chart was assessed by the c-statistic in the validation cohort. Thereafter the original score chart was updated based on the performance in the combined original and validation cohort with inclusion of celiac artery (CA) stenosis cause.
Results: In 8% of low-risk patients, 39% of intermediate-risk patients and 94% of high-risk patients of the validation cohort, CMI was diagnosed. Discriminative ability of the original model was acceptable (c-statistic 0.79). The total score of the updated chart ranged from 0 to 28 points (low risk 19% absolute CMI risk, intermediate risk 45%, and high risk 92%). The discriminative ability of the updated chart was slightly better (c-statistic 0.80).
Conclusion: The CMI prediction model performs and discriminates well in the validation cohort. The updated score chart has excellent discriminative ability and is useful in clinical decision making.

Gepubliceerd: United European Gastroenterol J 2019 Nov;7(9):1261-70
Impact factor: 3.453; Q2

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13. Covered stents versus Bare-metal stents in chronic atherosclerotic Gastrointestinal Ischemia (CoBaGI): study protocol for a randomized controlled trial
van Dijk LJD, Harki J, van ND, Verhagen HJM, Kolkman JJ, Geelkerken RH, Bruno MJ, Moelker A

Background: Chronic mesenteric ischemia (CMI) is the result of insufficient blood supply to the gastrointestinal tract and is caused by atherosclerotic stenosis of one or more mesenteric arteries in > 90% of cases. Revascularization therapy is indicated in patients with a diagnosis of atherosclerotic CMI to relieve symptoms and to prevent acute-on-chronic mesenteric ischemia, which is associated with high morbidity and mortality. Endovascular therapy has rapidly evolved and has replaced surgery as the first choice of treatment in CMI. Bare-metal stents (BMS) are standard care currently, although retrospective studies suggested significantly higher patency rates for covered stents (CS). The Covered stents versus Bare-metal stents in chronic atherosclerotic Gastrointestinal Ischemia (CoBaGI) trial is designed to prospectively assess the patency of CS versus BMS in patients with atherosclerotic CMI.

Methods/Design: The CoBaGI trial is a randomized controlled, parallel-group, patient- and investigator-blinded, superiority, multicenter trial conducted in six centers of the Dutch Mesenteric Ischemia Study group (DMIS). Eighty-four patients with a consensus diagnosis of atherosclerotic CMI are 1:1 randomized to either a balloon-expandable BMS (Palmaz Blue with rapid-exchange delivery system, Cordis Corporation, Bridgewater, NJ, USA) or a balloon-expandable CS (Advanta V12 over-the-wire, Atrium Maquet Getinge Group, Hudson, NH, USA). The primary endpoint is the primary stent-patency rate at 24 months assessed with CT angiography. Secondary endpoints are primary stent patency at 6 and 12 months and secondary patency rates, freedom from restenosis, freedom from symptom recurrence, freedom from re-intervention, quality of life according the EQ-5D-5 L and SF-36 and cost-effectiveness at 6, 12 and 24 months.
Discussion: The CoBaGI trial is designed to assess the patency rates of CS versus BMS in patients treated for CMI caused by atherosclerotic mesenteric stenosis. Furthermore, the CoBaGI trial should provide insights in the quality of life of these patients before and after stenting and its cost-effectiveness. The CoBaGI trial is the first randomized controlled trial performed in CMI caused by atherosclerotic mesenteric artery stenosis.
Trial Registration: ClinicalTrials.gov, ID: NCT02428582 . Registered on 29 April 2015.

Gepubliceerd: Trials 2019 Aug 20;20(1):519
Impact factor: 1.975; Q3

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14. Postponed or immediate drainage of infected necrotizing pancreatitis (POINTER trial): study protocol for a randomized controlled trial
van Grinsven J, van Dijk SM, Dijkgraaf MG, Boermeester MA, Bollen TL, Bruno MJ, vanBrunschot S., Dejong CH, van Eijck CH, van Lienden KP, Boerma D, van Duijvendijk P, Hadithi M, Haveman JW, van der Hulst RW, Jansen JM, Lips DJ, Manusama ER, Molenaar IQ, van der Peet DL, Poen AC, Quispel R, Schaapherder AF, Schoon EJ, Schwartz MP, Seerden TC, Spanier BWM, Straathof JW, Venneman NG, van de Vrie W, Witteman BJ, van Goor H, Fockens P, van Santvoort HC, Besselink MG

Background: Infected necrosis complicates 10% of all acute pancreatitis episodes and is associated with 15-20% mortality. The current standard treatment for infected necrotizing pancreatitis is the step-up approach (catheter drainage, followed, if necessary, by minimally invasive necrosectomy). Catheter drainage is preferably postponed until the stage of walled-off necrosis, which usually takes 4 weeks. This delay stems from the time when open necrosectomy was the standard. It is unclear whether such delay is needed for catheter drainage or whether earlier intervention could actually be beneficial in the current step-up approach. The POINTER trial investigates if immediate catheter drainage in patients with infected necrotizing pancreatitis is superior to the current practice of postponed intervention.
Methods: POINTER is a randomized controlled multicenter superiority trial. All patients with necrotizing pancreatitis are screened for eligibility. In total, 104 adult patients with (suspected) infected necrotizing pancreatitis will be randomized to immediate (within 24 h) catheter drainage or current standard care involving postponed catheter drainage. Necrosectomy, if necessary, is preferably postponed

until the stage of walled-off necrosis, in both treatment arms. The primary outcome is the Comprehensive Complication Index (CCI), which covers all complications between randomization and 6-month follow up. Secondary outcomes include mortality, complications, number of (repeat) interventions, hospital and intensive care unit (ICU) lengths of stay, quality-adjusted life years (QALYs) and direct and indirect costs. Standard follow-up is at 3 and 6 months after randomization.
Discussion: The POINTER trial investigates if immediate catheter drainage in infected necrotizing pancreatitis reduces the composite endpoint of complications, as compared with the current standard treatment strategy involving delay of intervention until the stage of walled-off necrosis.
Trial Registration: ISRCTN, 33682933 . Registered on 6 August 2015. Retrospectively registered.

Gepubliceerd: Trials 2019 Apr 25;20(1):239
Impact factor: 1.975; Q3

Totale impact factor: 64.729
Gemiddelde impact factor: 4.624

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 19.809
Gemiddelde impact factor: 9.905

Medical School

1. Patient's Skeletal Muscle Radiation Attenuation and Sarcopenic Obesity are Associated with Postoperative Morbidity after Neoadjuvant Chemoradiation and Resection for Rectal Cancer

Berkel AEM, Klaase JM, de Graaff F, Brusse-Keizer MGJ, Bongers BC, van Meeteren NLU

Background/Aims: To investigate the relation between skeletal muscle measurements (muscle mass, radiation attenuation, and sarcopenic obesity), postoperative morbidity, and survival after treatment of locally advanced rectal cancer.
Methods: This explorative retrospective study identified 99 consecutive patients who underwent neoadjuvant chemoradiation and surgery between January 2007 and May 2012. Skeletal muscle mass was measured as total psoas area and total abdominal muscle area (TAMA) at 3 anatomical levels using the patient's preoperative computed tomography scan. Radiation attenuation was measured using corresponding mean Hounsfield units for TAMA. Sarcopenic obesity was defined as body mass index above 25 kg.m-2 combined with skeletal muscle mass index below the sex-specific median. Postoperative complications were graded by using the -Clavien-Dindo classification.
Results: Twenty-five patients (25.3%) developed a grade 3-5 complication. Lower radiation attenuation was independently associated with overall ($p = 0.003$) and grade 3-5 complications ($p = 0.002$). Sarcopenic obesity was associated with overall complications (all $p < 0.05$). Skeletal muscle measurements and survival were not significantly related.
Conclusion: Radiation attenuation was associated with overall and grade 3-5 postoperative morbidity after neoadjuvant chemoradiation and non-laparoscopic resection for rectal cancer. Sarcopenic obesity was associated with overall complications.

Gepubliceerd: Dig Surg 2019;36(5):376-83
Impact factor: 1.884; Q2

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2. The Impact of Revascularisation on Quality of Life in Chronic Mesenteric Ischemia

Blauw JTM, Pastoors HAM, Brusse-Keizer M, Beuk RJ, Kolkman JJ, Geelkerken RH, For The Dutch Mesenteric Ischemia Study Group

Background: Chronic mesenteric ischemia (CMI) is characterized by long-standing abdominal symptoms due to insufficient mesenteric circulation. Data on the effect of revascularisation on quality of life (QoL) for CMI are scarce. This study is the first to evaluate the impact of revascularisation on quality of life.
Methods: Seventy-nine patients with CMI or acute-on-chronic mesenteric ischemia (AoCMI) underwent an intervention of one or more mesenteric arteries between January 2010 and July 2012. QoL before and after intervention was measured with the EuroQol-5D. Preintervention questionnaires were of standard care. Postintervention data were obtained by resending a questionnaire to the patients

between February and May 2013. To investigate the clinical relevance of our findings, the minimal clinically important difference (MCID) was used. Since there is no established MCID for CMI, we used the literature reference MCID of inflammatory bowel syndrome (IBS) of 0.074.
Results: Fifty-five (69.6%) of 79 patients returned their questionnaire and 23 (29.1%) were completely filled out. There was a significant increase of the median EQ-index score from 0.70 to 0.81 (p=0.02) and a significant reduction of symptoms in the domains usual activities (34.4%) and pain/discomfort (32.3%). There was a significant improvement of 17% in overall current health condition (VAS) (p=0.001). The MCID between baseline and postoperative EQ-5D index score was 0.162, indicating a clinically relevant improvement of quality of life after revascularisation.
Conclusion: Quality of life of CMI patients is improved after mesenteric artery revascularisation.

Gepubliceerd: Can J Gastroenterol Hepatol 2019;2019:7346013
Impact factor: 1.714; Q4

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3. Long-term Outcome of Surgery Versus Conservative Management for Recurrent and Ongoing Complaints After an Episode of Diverticulitis: 5-year Follow-up Results of a Multicenter Randomized Controlled Trial (DIRECT-Trial)
Bolkenstein HE, Consten ECJ, van der Palen J, Wall BJMV, Broeders IAMJ, Bemelman WA, Lange JF, Boermeester MA, Draaisma WA

Objective: The aim of this study was to establish whether surgical or conservative treatment leads to a higher quality of life (QoL) in patients with recurring diverticulitis and/or ongoing complaints. **Summary of background data:** The 6 months' results of the DIRECT trial, a randomized trial comparing elective sigmoidectomy with conservative management in patients with recurring diverticulitis (>2 episodes within 2 years) and/or ongoing complaints (>3 months) after an episode of diverticulitis, demonstrated a significantly higher QoL after elective sigmoidectomy. The aim of the present study was to evaluate QoL at 5-year follow-up.
Methods: From January 2010 to June 2014, 109 patients were randomized to either elective sigmoidectomy (N = 53) or conservative management (N = 56). In the present study, the primary outcome was QoL measured by the Gastrointestinal Quality of Life Index (GIQLI) at 5-year follow-up. Secondary outcome measures were SF-36 score, Visual Analogue Score (VAS) pain score, EuroQol-5D-3L (EQ-5D-3L) score, morbidity, mortality, perioperative complications, and long-term operative outcome.
Results: At 5-year follow-up, mean GIQLI score was significantly higher in the operative group [118.2 (SD 21.0)] than the conservative group [108.5 (SD 20.0)] with a mean difference of 9.7 (95% confidence interval 1.7-17.7). All secondary QoL outcome measures showed significantly better results in the operative group, with a higher SF-36 physical (P = 0.030) and mental score (P = 0.010), higher EQ5D score (P = 0.016), and a lower VAS pain score (P = 0.011). Twenty-six (46%) patients in the conservative group ultimately required surgery due to severe ongoing complaints. Of the operatively treated patients, 8 (11%) patients had anastomotic leakage and reinterventions were required in 11 (15%) patients.
Conclusion: Consistent with the short-term results of the DIRECT trial, elective sigmoidectomy resulted in a significantly increased QoL at 5-year follow-up compared

with conservative management in patients with recurring diverticulitis and/or ongoing complaints. Surgeons should counsel these patients for elective sigmoidectomy weighing superior QoL, less pain, and lower risk of new recurrences against the complication risk of surgery.

Gepubliceerd: Ann Surg 2018 Sep 20;269(4):612-20
Impact factor: 9.476; Q1

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4. Validation of the oxygen desaturation index in the diagnostic workup of obstructive sleep apnea
Fabius TM, Benistant JR, Bekkedam L, van der Palen J, de Jongh FHC, Eijsvogel MMM

Introduction: Obstructive sleep apnea (OSA) is common, and diagnosis requires expensive and laborious testing to assess the apnea hypopnea index (AHI). We performed an analysis to explore the relationship between the oxygen desaturation index (ODI) as measured with pulse oximetry and the AHI in our large portable monitoring (PM) database to find an optimal cutoff value for the ODI in order to be able to exclude AHI >/= 5 on PM.
Methods: Three thousand four hundred thirteen PM recordings were randomly divided into a training set (N = 2281) and a test set (N = 1132). The optimal cutoff for the ODI to exclude an AHI >/= 5 on PM was determined in the training set and subsequently validated in the test set.
Results: Area under the curve of the ODI to exclude an AHI >/= 5 on PM was 0.997 in the training set and 0.996 in the test set. In the training set, the optimal cutoff to predict an AHI < 5 was an ODI < 5. Using this cutoff in the test set provided a sensitivity of 97.7%, a specificity of 97.0%, a positive predictive value of 99.2%, and a negative predictive value of 91.4%.
Conclusion: An ODI < 5 predicts an AHI < 5 with high sensitivity and specificity when measured simultaneously using the same oximeter during PM recording.

Gepubliceerd: Sleep Breath 2019;23(1):57-63
Impact factor: 2.326; Q3

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5. pH-responsive materials for optical monitoring of wound status
Gamerith C, Luschnig D, Ortner A, Pietrzik N, Guse JH, Burnet M, Haalboom M, van der Palen J, Heinzle A, Sigl E, Gübitz GM

The monitoring of infection status of wounds is an emerging field and the pH of wound exudate is considered one potential indicator of infection. pH indicators intended for use in medical devices, such as swabs or dressings, need to be fixed in place, however, visual pH indicators are usually soluble molecules so are not inherently suitable for use in devices. To address this, we developed a rapid and simple immobilisation method for coupling pH-responsive dyes onto solid phases. The use of a silane based coupling agent for immobilisation of bromocresol purple led to a shift in the pH dependent spectral properties of the resulting material. The pH responsive material changes from yellow to green to blue with rising pH providing an ideal contrast to the reddish colour of most wound exudates. This is a key advantage

over currently available alternatives when considering the suitability of this material for incorporation into various medical devices. In addition, we analysed clinical study samples to verify the association between wound infection and elevated pH-values. A device with an embedded indicator that changes to a contrast colour could represent a simple and easy-to-use system for detecting wounds at risk of infection..

Gepubliceerd: Sensors and Actuators B: Chemical 2019;301:126966
Impact factor: 6.393; Q1

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6. Body weight course in the DIAbetes and LifEstyle Cohort Twente (DIALECT-1)-A 20-year observational study
Gant CM, Mensink I, Binnenmars SH, van der Palen JAM, Bakker SJL, Navis G, Laverman GD

Background: Although weight gain increases risk of type 2 diabetes, real-life data on the weight course in patients with established type 2 diabetes are scarce. We assessed weight course in a real-life diabetes secondary care setting and analyzed its association with patient characteristics, lifestyle habits and initiation of insulin, glucagon like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose co-transporter-2 inhibitors (SGLT-2i).
Methods: Data on weight, insulin, GLP-1 RA and SGLT-2i use were collected retrospectively (12 years) and prospectively (8 years) from patients included in the DIAbetes and LifEstyle Cohort Twente-1 (DIALECT-1, n = 450, age 63 +/- 9 years, 58% men, diabetes duration [7-18] years). Lifestyle habits were assessed using validated questionnaires. The association of clinical parameters with body mass index (BMI) course was determined using linear mixed models. Patients who underwent bariatric surgery (n = 19) had a distinct BMI course and were excluded from the study.
Results: Baseline BMI was 31.3 (0.3) and was higher in women, patients aged <60 years and patients with unfavorable lifestyle habits. BMI increased to 32.5 (0.3) after 12 years (P<0.001), and thereafter decreased to 31.5 (0.3) after 20 years, resulting in a similar BMI as the baseline BMI (P = 0.96, compared to baseline). Clinical parameters or initiation of insulin or SGLT-2i were not associated with BMI course. Patients who initiated GLP-1 RA declined in BMI compared to non-users (Pinteraction = 0.003).
Conclusions: High BMI that real-life patients with type 2 diabetes gained earlier in life, remained stable in the following decades. Weight loss interventions should remain a priority, and GLP-1 RA might be considered to support weight loss.

Gepubliceerd: PLoS One 2019;14(6):e0218400
Impact factor: 2.776; Q2

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7. Culture results from wound biopsy versus wound swab: does it matter for the assessment of wound infection?
Haalboom M, Blokhuis-Arkes MHE, Beuk RJ, Meerwaldt R, Klont R, Schijffelen MJ, Bowler PB, Burnet M, Sigl E, van der Palen J

Objectives: The aim of this study was to determine whether assessment of wound infection differs when culture results from wound biopsy versus wound swab are available in clinical practice.
Methods: For 180 eligible patients, a swab and biopsy were taken from one wound during a regular appointment at a wound care facility in eastern Netherlands. Culture results from both methods were supplemented with clinical information and provided to a panel of six experts who independently assessed each wound as infect or not, separately for swab and biopsy. Assessments for biopsy and swab were compared for the complete expert panel, and for individual experts.
Results: The complete expert panel provided the same wound assessment based on (clinical information and) culture results from wound biopsy and wound swab in 158 of 180 wounds (87.8%, kappa 0.67). For individual experts, agreement between biopsy and swab varied between 77% and 96%. However, there were substantial differences between experts: the same assessment was provided in 62 (34.4%) to 76 (42.2%) wounds for swab and biopsy respectively.
Conclusions: Assessment of infection does not significantly differ when culture results from swabs or biopsies are available. The substantial variability between individual experts indicates non-uniformity in the way wounds are assessed. This complicates accurate detection of infection and comparability between studies using assessment of infection as reference standard.

Gepubliceerd: Clin Microbiol Infect 2019;25(5):629.e7-629.e12
Impact factor: 6.425; Q1

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8. Differentiation between infected and non-infected wounds using an electronic nose
Haalboom M, Gerritsen JW, van der Palen J

Objectives: The aim of this study was to explore whether an electronic nose, Aetholab, is able to discriminate between infected versus non-infected wounds, based on headspace analyses from wound swabs.
Methods: A total of 77 patients participated in this pilot study. Each wound was assessed for infection based on clinical judgment. Additionally, two wound swabs were taken, one for microbiological culture and one for measurement with Aetholab. Diagnostic properties with 95% confidence intervals (95%CIs) of Aetholab were calculated with clinical judgment and microbiological culture results as reference standards.
Results: With clinical judgment as reference standard, Aetholab had a sensitivity of 91% (95%CI 76-98) and a specificity of 71% (95%CI 55-84). Diagnostic properties were somewhat lower when microbiological culture results were used as reference standard: sensitivity 81% (95%CI 64-91), specificity 63% (95%CI 46-77).
Conclusions: Aetholab seems a promising diagnostic tool for wound infection given the diagnostic properties presented in this pilot study. A larger study is needed to confirm our results.

Gepubliceerd: Clin Microbiol Infect 2019 Oct;25(10):1288
Impact factor: 6.425; Q1

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9. A randomized controlled efficacy study of the Medido medication dispenser in Parkinson's disease
Hannink K, Ter Brake L, Oonk NGM, Wertenbroek AA, Piek M, Vree-Egberts L, Faber MJ, van der Palen J, Dorresteijn LD

Background: Complex medication schedules in Parkinson's disease (PD) result in lower therapy adherence, which contributes to suboptimal therapy and clinical deterioration. Medication reminder systems might improve therapy adherence and subsequently improve symptoms of PD. This randomized controlled study assessed the effect of the electronic medication dispenser Medido on physical disability in PD, as a proxy for changes in therapy adherence.x
Methods: Eighty-seven patients were randomized into the Medido group or control group. The primary outcome of physical disability was measured by the AMC Linear Disability Scale (ALDS). Secondary outcomes were quality of life (QoL) (PDQ-39), health status (EQ5D-5L, VAS), non-motor symptoms (NMS-Quest), and QoL of the caregiver (PDQ-carer). Measurements were performed at baseline, and after 3 and 6 months follow-up.
Results: When using the Medido, a non-significant improvement of 3.0 points (95% CI -5.6;11.6) was seen in ALDS. The exploratory subgroup Hoehn & Yahr classification (H&Y) > 2.5 improved significantly on ALDS with 14.7 points (95% CI -28.5;-0.9, p = 0.029 for group x time interaction). QoL deteriorated with 1.0 point in PDQ-39 (p = 0.01 for group x time interaction) in favor of the control group. Non-significant differences were observed for VAS (0.4 points, p = 0.057) and NMS-Quest (1.3 points, p = 0.095) in favor of the Medido group. No changes over time were observed in EQ5D-5L and PDQ-carer.
Conclusions: Based on these data, no firm conclusion can be drawn, but use of the Medido medication dispenser may result in a clinical improvement of physical disability and seems particularly appropriate for more severe patients.
Trial Registration: NTR3917 . Registered 19 March 2013.

Gepubliceerd: BMC Geriatr 2019 Oct 16;19(1):273
Impact factor: 2.818; Q1

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10. Breast-conserving therapy in older patients with breast cancer over three decades: progress or stagnation
Jobsen JJ, Middelburg JG, van der Palen J, Riemersma S, Siemerink E, Struikmans H, Siesling S

Background: The aim of this study was to analyze the distant metastases-free survival (DMFS), and disease-specific survival (DSS) after breast-conserving therapy (BCT) in older patients with breast cancer in a large, population-based, single-center cohort study with long-term follow-up.
Material and methods: Analyses were based on 1,425 women aged 65years and older with breast cancer treated with BCT. Patients were divided in three age categories: 65 - 70years, 71 - 75years, and >75years. The study period extended over 30 years, divided in three decades. Multivariate survival analysis was carried out using Cox regression analysis.
Results: The two youngest age categories showed significant improvements over time in 12-year DMFS and DSS. For women aged 65 - 70years, this improvement

was noted in stage I and stage II disease, while for women aged 71 - 75years this was mainly in stage II tumors. Women >75 years of age did not show any improvement over time, regardless of stage.
Conclusion: Among older Dutch women with breast cancer, outcomes with regard to DMFS and DSS after BCT differ between various age categories, showing the least gain in the very old.

Gepubliceerd: J Geriatr Oncol 2019;10(2):330-6
Impact factor: 3.164; Q2

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11. Effects of European Society of Cardiology guidelines on medication profiles after hospitalization for heart failure in 22,476 Dutch patients: from 2001 until 2015
Kruik-Kolloffel WJ, Linssen GCM, Kruik HJ, Movig KLL, Heintjes EM, van der Palen J

Prescriber adherence to guideline-recommended medication in patients with heart failure (HF) in clinical practice is suboptimal. We analyzed how evolving guideline recommendations influenced medication profiles after a first HF hospitalization. We extracted medication profiles from the Dutch PHARMO Database Network for 22,476 patients with a diagnosis of HF at hospital discharge between 2001 and 2015. The percentage of patients prescribed the combination of a beta-blocker (BB) and an angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB) increased from 24 to approximately 45% within this 15-year period. The percentage of patients who also used a mineralocorticoid-receptor antagonist (MRA) reached approximately 20%. The probability of being prescribed these combinations decreased with increasing age. As a consequence of the policy change in the ESC guideline 2001, the use of BB increased from less than 40% in 2001 to about 70% by 2015. The percentage of patients prescribed an ACEI and/or an ARB, an MRA, or a diuretic was about stable, at respectively 63%, 37%, and 82%. Although the 2012 ESC guideline also advised MRA in the New York Heart Association (NYHA) class II, there was no increase in MRA prescriptions. Compliance with the ESC guidelines varied for the individual recommendations. Remarkably, there was no significant increase in MRA prescriptions. At the same time, developments were demonstrated, which were not instigated by the guidelines, like the shift from ACEI to ARB. Although the exact HF classification of our patients was unknown, given a relatively stable case mix, our data provide insight into "real-world" pharmacological management.

Gepubliceerd: Heart Fail Rev 2019 Jul;24(4):499-510
Impact factor: 4.015; Q2

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12. Assessing Exercise-Induced Bronchoconstriction in Children; The Need for Testing
Lammers N, van Hoesel MHT, Kamphuis M, Brusse-Keizer M, van der Palen J, Visser R, Thio BJ, Driessen JMM

Objective: Exercise-induced bronchoconstriction (EIB) is a specific morbidity of childhood asthma and a sign of insufficient disease control. EIB is diagnosed and monitored based on lung function changes after a standardized exercise challenge

test (ECT). In daily practice however, EIB is often evaluated with self-reported respiratory symptoms and spirometry. We aimed to study the capacity of pediatricians to predict EIB based on information routinely available during an outpatient clinic visit.
Methods: A clinical assessment was performed in 20 asthmatic children (mean age 11.6 years) from the outpatient clinic of the MST hospital from May 2015 to July 2015. During this assessment, video images were made. EIB was measured with a standardized ECT performed in cold, dry air. Twenty pediatricians (mean years of experience 14.4 years) each evaluated five children, providing 100 evaluations, and predicted EIB severity based on their medical history, physical examination, and video images. EIB severity was predicted again after additionally providing baseline spirometry results.
Results: Nine children showed no EIB, four showed mild EIB, two showed moderate, and five showed severe EIB. Based on clinical information and spirometry results, pediatricians detected EIB with a sensitivity of 84% (95% CI 72-91%) and a specificity of 24% (95% CI 14-39%).The agreement between predicted EIB severity classifications and the validated classifications after the ECT was slight [Kappa = 0.05 (95% CI 0.00-0.17)]. This agreement still remained slight when baseline spirometry results were provided [Kappa = 0.19 (95% CI 0.06-0.32)].
Conclusion: Pediatricians' prediction of EIB occurrence was sensitive, but poorly specific. The prediction of EIB severity was poor. Pediatricians should be aware of this in order to prevent misjudgement of EIB severity and disease control.

Gepubliceerd: Front Pediatr 2019;7:157
Impact factor: 2.349; Q2

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13. Exacerbation action plans for patients with COPD and comorbidities: a randomised controlled trial
Lenferink A, van der Palen J, van der Valk PDLP, Cafarella P, van Veen A, Quinn S, Groothuis-Oudshoorn CGM, Burt MG, Young M, Frith PA, Effing TW

This international randomised controlled trial evaluated whether COPD patients with comorbidities, trained in using patient-tailored multidisease exacerbation action plans, had fewer COPD exacerbation days than usual care (UC).COPD patients (Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification II-IV) with >/=1 comorbidity (ischaemic heart disease, heart failure, diabetes, anxiety, depression) were randomised to a patient-tailored self-management intervention (n=102) or UC (n=99). Daily symptom diaries were completed for 12 months. The primary outcome "COPD exacerbation days per patient per year" was assessed using intention-to-treat analyses.No significant difference was observed in the number of COPD exacerbation days per patient per year (self-management: median 9.6 (interquartile range (IQR) 0.7-31.1); UC: median 15.6 (IQR 3.0-40.3); incidence rate ratio (IRR) 0.87 (95% CI 0.54; 1.39); p=0.546). There was a significantly shorter duration per COPD exacerbation for self-management (self-management: median 8.1 (IQR 4.8-10.1) days; UC: median 9.5 (IQR 7.0-15.1) days; p=0.021), with no between-group differences in the total number of respiratory hospitalisations (IRR 0.76 (95% CI 0.42; 1.35); p=0.348), but a lower probability of >/=1 for respiratory-related hospitalisation compared to UC (relative risk 0.55 (95% CI 0.35; 0.87); p=0.008). No between-group differences were observed in all-cause hospitalisations (IRR 1.07 (95% CI 0.66; 1.72)) or mortality (self-management: n=4 (3.9%); UC: n=7 (7.1%); relative risk 0.55

(95% CI 0.17; 1.84)).Patient-tailored exacerbation action plans for COPD patients with comorbidities did not significantly reduce exacerbation days, but reduced the duration per COPD exacerbation and the risk of having at least one respiratory-related hospitalisation during follow-up, without excess all-cause mortality.

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Impact factor: 11.807; Q1

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14. Shorter cryoballoon applications times do effect efficacy but result in less phrenic nerve injury: Results of the randomized 123 study
Molenaar MMD, Timmermans CC, Hesselink T, Scholten MF, Ter Bekke RMA, Luermans JGLM, Brusse-Keizer M, Kraaier K, Ten Haken B, Grandjean JG, Vernooy K, van Opstal JM

Background: The second-generation cryoballoon significantly improves outcome of pulmonary vein isolation (PVI) but may cause more complications than the first generation. Currently, no consensus regarding optimal cryoballoon application time exists. The 123-study aimed to assess the minimal cryoballoon application duration necessary to achieve PVI (primary endpoint) and the effect of application duration on prevention of phrenic nerve injury (PNI).
Methods: Patients <75 years of age with paroxysmal atrial fibrillation, normal PV anatomy, and left atrial size <40 cc/m(2) or <50 mm were randomized to two applications of different duration: "short," "medium," or "long." A total of 222 patients were enrolled, 74 per group.
Results: Duration per application was 105 (101-108), 164 (160-168), and 224 (219-226) s and isolation was achieved in 79, 89, and 90% ($P < 0.001$) of the PVs after two applications in groups short, medium, and long, respectively. Only for the left PVs, the success rate of the short group was significantly less compared to the medium- and long-duration groups ($P < 0.001$). PNI during the procedure occurred in 19 PVs (6.5%) in the medium and in 20 PVs (6.8%) in the long duration groups compared to only five PVs (1.7%) in the short duration group ($P < 0.001$).
Conclusions: Short cryoballoon ablation application times, less than 2 min, did affect the success for the left PVs but not for the right PVs and resulted in less PNI. A PV tailored approach with shorter application times for the right PVs might be advocated.

Gepubliceerd: Pacing Clin Electrophysiol 2019 May;42(5):508-14
Impact factor: 1.340; Q4

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15. Effect of long-term use of ankle-foot orthoses on tibialis anterior muscle electromyography in patients with sub-acute stroke: a randomized controlled trial
Nikamp C, Buurke J, Schaake L, van der Palen J, Rietman J, Hermens H

Objective: To determine: (i) whether the use of ankle-foot orthoses over a period of 26 weeks affects tibialis anterior muscle activity; (ii) whether the timing of provision of ankle-foot orthoses (early or delayed) affects the results; (iii) whether the provision of ankle-foot orthoses affects tibialis anterior muscle activity within a single measurement.

Design: Randomized controlled trial. SUBJECTS: Unilateral hemiparetic subjects, a maximum of 6 weeks post-stroke.
Methods: Subjects were assigned randomly to early (at inclusion; week 1) or delayed provision of ankle-foot orthoses (8 weeks later; week 9). Tibialis anterior electromyography was measured with and without ankle-foot orthoses, in study weeks 1, 9, 17 and 26.
Results: A total of 26 subjects were analysed. In a single measurement, use of an ankle-foot orthosis significantly reduced the activity levels of the tibialis anterior muscle during the swing phase ($p = 0.041$) compared with walking without an ankle-foot or-thosis. During the 26-week follow-up, no changes were found in tibialis anterior muscle activity in the swing phase without an ankle-foot orthosis, both within-groups ($p = 0.420$ early; $p = 0.282$ delayed), and between-groups ($p = 0.987$). After 26 weeks, no differences were found in tibialis anterior muscle activity between both groups in the swing phase, with ($p = 0.207$) or without ankle-foot orthoses ($p = 0.310$).
Conclusion: Use of ankle-foot orthoses post-stroke reduced tibialis anterior muscle activity in the swing phase within 1 measurement; however, long-term use of ankle-foot orthoses for 26 weeks did not affect such activity. Early or delayed provision of ankle-foot orthoses did not affect the findings. The results indicate that there is no need to fear negative consequences on tibialis anterior-activity because of long-term AFO-use (early) after stroke.

Gepubliceerd: J Rehabil Med 2019;51(1):11-7
Impact factor: 1.907; Q2

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16. The effect of ankle-foot orthoses on fall/near fall incidence in patients with (sub-)acute stroke: A randomized controlled trial
Nikamp CDM, Hobbelink MSH, van der Palen J, Hermens HJ, Rietman JS, Buurke JH

Falls are commonly reported post-stroke. Ankle-foot orthoses (AFOs) are often provided to improve safety and walking, but the effect of their use in the reduction of falls after stroke is unknown. A randomized controlled trial (RCT) on the effects of AFO-provision after stroke was performed. Effects on clinical scales, 3D-gait kinematics and muscle-activity were previously reported. This paper aims to study the effects of AFO-provision on occurrence and circumstances of falls/near falls. The RCT included unilateral hemiparetic stroke patients. AFOs were provided either early (study week 1) or delayed (study week 9). Both groups were compared in the first eight weeks of the study and diaries were used to register falls/near falls and their circumstances. Follow-up measurements were performed in week 9-52, in which both groups were provided with AFOs. Functional Ambulation Categories and Berg Balance Scale were assessed to determine walking independence and balance, respectively. Last known scores were noted in case of an incident. Thirty-three subjects were included (16 early, 17 delayed). In week 1-8, the early group, who were provided with AFOs, fell significantly more frequently compared with the delayed group, 11 versus 4 times, respectively (Incidence Rate Ratio = 2.9, $p = 0.039$). Out of the falls recorded in the early group, 63.6% occurred without wearing AFOs. Most of these falls occurred during transfers (36.4%) and standing (27.3%), and notably it were the subjects who did not have independent walking ability. No differences were found for near falls in week 1-8, or for falls/near falls in week 9-52. Six severe

consequences (including fractures) were reported from a fall. To conclude, the subjects provided with AFOs early after stroke reported a higher number of falls, compared to the subjects that had not yet been provided with AFOs. However, in the subjects provided with AFOs, 63.6% of the falls occurred whilst without wearing the AFO. Furthermore, the majority of these incidents took place whilst subjects had no independent walking ability. This raises an interesting question of the importance of careful instructions to patients and their relatives, and the influence of potential cognitive impairments on the ability of the subjects to take on these instructions.

Gepubliceerd: PLoS One 2019;14(3):e0213538
Impact factor: 2.776; Q2

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17. The effect of a structured medication review on quality of life in Parkinson's disease: The study protocol
Oonk NGM, Movig KLL, Munster EM, Koehorst-Ter Huurne K, van der Palen J, Dorresteijn LDA

Background: Treatment of Parkinson's disease (PD) is symptomatic and frequently consists of complicated medication regimes. This negatively influences therapy adherence, resulting in lower benefit of treatment, drug related problems and decreased quality of life (QoL). A potential effective intervention strategy is a structured medication review, executed by community pharmacists. However, little is known about the effects on clinical endpoints like QoL, as well as on feasibility and cost-effectiveness in PD patients. Objectives: To assess the effect of a structured medication review on QoL in PD patients. Secondary objectives are measurements of physical disability, activities in daily life, non-motor symptoms, health state, personal carers' QoL and cost-effectiveness. Furthermore, a better insight in the process of performing medication reviews will be obtained from the perspective of community pharmacists.
Methods: In this multicenter randomized controlled trial we aim to enroll 200 PD patients from the outpatient clinic of three Dutch hospitals. Community pharmacists will perform a structured medication review in half of the assigned patients; the other half will receive usual care. Data obtained by use of six validated questionnaires will be collected at baseline and after 3 and 6 months of follow-up. Semi-structured interviews with community pharmacists will be conducted till data saturation has been reached.
Discussion: This trial targets a high-risk patient group for whom optimizing therapy by a structured medication review might be of added value. If effectiveness is proven, this could further promote the implementation of pharmaceutical care in a primary care setting.

Gepubliceerd: Contemp Clin Trials Commun 2019 Mar;13:100308
Impact factor: 0; nvt

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18. Development and evaluation of a tailored e-self-management intervention (dr. Bart app) for knee and/or hip osteoarthritis: study protocol
Pelle T, Bevers K, van der Palen J, van den Hoogen FHJ, van den Ende CHM

Background: This paper describes (the development of) an eHealth tool (dr. Bart app) to enhance self-management and to optimize non-surgical health care utilization in patients with knee and/or hip osteoarthritis (OA) and presents a study aiming 1) to study the effectiveness of the dr. Bart app on health care use 2) to explore differences in use, usability and the clinical outcomes of the dr. Bart app between the Netherlands and Germany.
Methods: The dr. Bart app is a fully automated eHealth application and is based on the Fogg model for behavioural change, augmented with reminders, rewards and self-monitoring to reinforce app engagement and health behaviour. The dr. Bart app propose goals to a healthier lifestyle based on machine learning techniques fed by data collected in a personal profile and choosing behaviour of the app user. Patients >/=50 years with self-reported knee and/or hip OA will be eligible to participate. Participants will be recruited in the community through advertisements in local newspapers and campaigns on social media. This protocol presents a study with three arms, aiming to include 161 patients in each arm. In the Netherlands, patients are randomly allocated to usual care or dr. Bart app and in Germany all patients receive the dr. Bart app. The primary outcome of the first research question is the number of self-reported consultations in secondary health care. The primary outcome of the second research question (comparison between the Netherlands and Germany) is self-management behaviour assessed by the patient activation measure (PAM-13) questionnaire. Secondary outcomes are costs, health-related quality of life, physical functioning and activity, pain, use and usability of the dr. Bart app. Data will be collected through three online questionnaires (at baseline and after 3 and 6 months after inclusion).
Discussion: This study will gain insight into the effectiveness of the dr. Bart app in the (conservative) treatment of patients with knee and/or hip OA and differences in the use and usability of the dr. Bart app between the Netherlands and Germany.
Trial Registration: Dutch Trial Register (Trial Number NTR6693 / NL6505). Registration date: 4 September 2017.

Gepubliceerd: BMC Musculoskelet Disord 2019 Aug 31;20(1):398
Impact factor: 2.002; Q2

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19. Incidence and Treatment of Limb Occlusion of the Anaconda Endograft After Endovascular Aneurysm Repair
Rodel SGJ, Zeebregts CJ, Meerwaldt R, van der Palen J, Geelkerken RH

Purpose: To evaluate the incidence and treatment of limb occlusions of the second- and third-generation Anaconda endografts.
Methods: A single-center retrospective study was conducted involving 317 consecutive patients (mean age 76 years; 289 men) who underwent endovascular aneurysm repair for elective asymptomatic, symptomatic intact, and ruptured infrarenal abdominal aortic aneurysm with 2 versions of the Anaconda device. From September 2003 to July 2011, the second-generation device was used in 189 patients (mean age 77 years; 169 men) and from July 2011 to September 2015, the third-generation device was implanted in 128 patients (mean age 75 years; 120 men). The rates of limb occlusion were compared between groups and according to compliance with the instructions for use (IFU); predictors were sought in multivariate

analysis. The results of the latter are given as the hazard ratio (HR) and 95% confidence interval (CI).
Results: Kaplan-Meier freedom of occlusion estimates for second- and third-generation devices, respectively, was 96.6% and 95.0% at 1 year, 89.9% and 95.0% at 2 years, and 86.5% and 88.6% at 5 years. There was no significant difference in overall occlusion rate between the second-generation devices (p=0.332) or with regard to use within the IFU (p=0.827); however, there was a clinically relevant decrease in the occlusion rate for elective patients treated with the third-generation device (6.4% vs 13.1%, p=0.077). There was an increase in the occlusion rate when the iliac limb diameter was </=13 mm. In multivariate analysis, the only independent predictor of limb occlusion was a small distal prosthesis diameter (HR 0.732, 95% CI 0.63 to 0.86, p<0.001). Symptomatic nonruptured and ruptured abdominal aortic aneurysm (AAA) interventions had an almost 2-fold increased risk of occlusion (HR 1.95, 95% CI 0.93 to 4.11, p=0.078), though this did not reach statistical significance.
Conclusion: The Anaconda design has proven effectiveness in AAA exclusion in daily practice inside the IFU. However, efforts could be made to further reduce the limb occlusion rate.

Gepubliceerd: J Endovasc Ther 2019 Feb;26(1):113-20
Impact factor: 2.986; Q1

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20. Comparison of outcome in stroke patients admitted during working hours vs. off-hours; a single-center cohort study
Tuinman MP, van Golde EGA, Portier RP, Knottnerus ILH, van der Palen J, den Hertog HM, Brouwers PJAM

Introduction: We aimed to disprove an in-hospital off-hour effect in stroke patients by adjusting for disease severity and poor prognostic findings on imaging.
Patients and methods: Our study included 5378 patients from a single center prospective stroke registry of a large teaching hospital in the Netherlands, admitted between January 2003 and June 2015. Patients were categorized by admission time, off-hours (OH) or working hours (WH). The in-hospital mortality, 7-day mortality, unfavorable functional outcome (modified Rankin scale > 2) and discharge to home were analyzed. Results were adjusted for age, sex, stroke severity (NIHSS score) and unfavorable findings on imaging of the brain (midline shift and dense vessel sign).
Results: Overall, 2796 patients (52%) were admitted during OH, which had a higher NIHSS score [3 (IQR 2-8) vs. 3 (IQR 2-6): p < 0.01] and had more often a dense vessel sign at admission (7.9% vs. 5.4%: p < 0.01). There was no difference in mortality between the OH-group and WH-group (6.2% vs. 6.0%; p = 0.87). The adjusted hazard ratio of in-hospital mortality during OH was 0.87 (95% CI: 0.70-1.08). Analysis of 7-day mortality showed similar results. Unadjusted, the OH-group had an unfavorable outcome [OR: 1.14 (95% CI: 1.02-1.27)] and could less frequently be discharged to home [OR: 1.16 (95% CI: 1.04-1.29)], which was no longer present after adjustment. DISCUSSION AND
Conclusions: The overall outcome of stroke patients admitted to a large Dutch teaching hospital is not influenced by time of admission. When studying OH effects, adjustment for disease severity and poor prognostic findings on imaging is crucial before drawing conclusions on staffing and material.

Gepubliceerd: J Neurol 2019;266(3):782-9
Impact factor: 4.204; Q1

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21. Does exercise-induced bronchoconstriction affect physical activity patterns in asthmatic children?
van der Kamp MR, Thio BJ, Tabak M, Hermens HJ, Driessen J, van der Palen J

Exercise-induced bronchoconstriction (EIB) is a sign of uncontrolled childhood asthma and classically occurs after exercise. Recent research shows that EIB frequently starts during exercise, called breakthrough-EIB (BT-EIB). It is unknown whether this more severe type of EIB forces children to adapt their physical activity (PA) pattern in daily life. Therefore, this pilot study aims to investigate daily life PA (amount, intensity, duration, and distribution) in children with BT-EIB, 'classic' EIB, and without EIB. A Fitbit Zip activity tracker was used for one week to objectively measure daily life PA at one-minute intervals. Thirty asthmatic children participated. Children with BT-EIB were less physically active compared to children without EIB (respectively 7994 and 11,444 steps/day, p = .02). Children with BT-EIB showed less moderate-to-vigorous PA compared to the children without (respectively 117 and 170 minutes/day, p = .02). Children with EIB (both BT and classic) had significant shorter bouts of activity and a less stretched distribution of bout lengths compared to the non-EIB group (all p < .05). These results emphasize a marked association between EIB severity and PA patterns in daily life, stressing the need for a thorough clinical evaluation of exercise-induced symptoms in childhood asthma.

Gepubliceerd: J Child Health Care 2019 Oct 13;1367493519881257
Impact factor: 1.505; Q2

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22. Effect of diet with or without exercise on abdominal fat in postmenopausal women - a randomised trial
van Gemert WA, Peeters PH, May AM, Doornbos AJH, Elias SG, van der Palen J, Veldhuis W, Stapper M, Schuit JA, Monninkhof EM

Background: We assessed the effect of equivalent weight loss with or without exercise on (intra-) abdominal fat in postmenopausal women in the SHAPE-2 study.
Methods: The SHAPE-2 study is a three-armed randomised controlled trial conducted in 2012-2013 in the Netherlands. Postmenopausal overweight women were randomized to a diet (n = 97), exercise plus diet (n = 98) or control group (n = 48). Both intervention groups aimed for equivalent weight loss (6-7%) following a calorie-restricted diet (diet group) or a partly supervised intensive exercise programme (4 h per week) combined with a small caloric restriction (exercise plus diet group). Outcomes after 16 weeks are amount and distribution of abdominal fat, measured by magnetic resonance imaging (MRI) with the use of the three-point IDEAL Dixon method.
Results: The diet and exercise plus diet group lost 6.1 and 6.9% body weight, respectively. Compared to controls, subcutaneous and intra-abdominal fat reduced significantly with both diet (- 12.5% and - 12.0%) and exercise plus diet (- 16.0% and - 14.6%). Direct comparison between both interventions revealed that the reduction in

subcutaneous fat was statistically significantly larger in the group that combined exercise with diet: an additional 10.6 cm(2) (95%CI -18.7; - 2.4) was lost compared to the diet-only group. Intra-abdominal fat loss was not significantly larger in the exercise plus diet group (- 3.8 cm(2), 95%CI -9.0; 1.3).
Conclusions: We conclude that weight loss of 6-7% with diet or with exercise plus diet reduced both subcutaneous and intra-abdominal fat. Only subcutaneous fat statistically significantly reduced to a larger extent when exercise is combined with a small caloric restriction.
Trial register: NCT01511276 (clinicaltrials.gov), prospectively registered.

Gepubliceerd: BMC Public Health 2019 Feb 11;19(1):174
Impact factor: 2.567; Q2

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23. Radiation exposure in an endovascular aortic aneurysm repair program after introduction of a hybrid operating theater
Wermelink B, Willigendael EM, Smit C, Beuk RJ, Brusse-Keizer M, Meerwaldt R, Geelkerken RH

Background: A hybrid operating theater (HOT) enables optimal image quality, improved ergonomics, and excellent sterility for complex endovascular and hybrid procedures. We hypothesize that the commissioning of a new HOT involves a learning curve. It is unclear how steep the learning curve of these advanced HOTs is. The main purpose of this research was to evaluate radiation exposure parameters in a new HOT for a team of vascular surgeons experienced with infrarenal endovascular aneurysm repair (EVAR) procedures in a conventional operating room with a mobile C-arm. In addition, a comparison of the dose-area product (DAP) achieved in this study and in the literature was made.
Methods: Before commissioning of the HOT, four vascular surgeons completed a comprehensive HOT training program. From the commissioning of the HOT, clinical and procedural data for all consecutive acute and elective patients treated with EVAR were retrospectively collected for a period of 18 months (January 2016-June 2017). A literature review was conducted of the dose-area product in EVAR procedures performed with a dedicated fixed system or mobile C-arm to analyze how this study performed compared with the literature.
Results: In the 18-month study period, 77 patients were treated with EVAR (59 electively and 18 acutely), from whom the data were obtained. There was no significant change in radiation exposure parameters over time. From the commissioning of the HOT, EVAR procedures were performed with radiation exposure parameters similar to those of studies found in experienced vascular centers using fixed systems.
Conclusions: Concerning radiation exposure parameters, the commissioning of a new HOT was not accompanied by a learning curve. Radiation exposure parameters achieved in this study were similar to those of studies from experienced and dedicated vascular centers.

Gepubliceerd: J Vasc Surg 2019 Dec;70(6):1927-34
Impact factor: 3.243; Q1

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24. Effect of physical exercise on cognitive function and brain measures after chemotherapy in patients with breast cancer (PAM study): protocol of a randomised controlled trial
Witlox L, Schagen SB, de Ruiter MB, Geerlings MI, Peeters PHM, Koevoets EW, van der Wall E, Stuiver M, Sonke G, Velthuis MJ, van der Palen J, Jobsen JJ, May AM, Monninkhof EM

Introduction: After treatment with chemotherapy, many patients with breast cancer experience cognitive problems. While limited interventions are available to improve cognitive functioning, physical exercise showed positive effects in healthy older adults and people with mild cognitive impairment. The Physical Activity and Memory study aims to investigate the effect of physical exercise on cognitive functioning and brain measures in chemotherapy-exposed patients with breast cancer with cognitive problems.
Methods and analytics: One hundred and eighty patients with breast cancer with cognitive problems 2-4 years after diagnosis are randomised (1:1) into an exercise intervention or a control group. The 6-month exercise intervention consists of twice a week 1-hour aerobic and strength exercises supervised by a physiotherapist and twice a week 1-hour Nordic or power walking. The control group is asked to maintain their habitual activity pattern during 6 months. The primary outcome (verbal learning) is measured at baseline and 6 months. Further measurements include online neuropsychological tests, self-reported cognitive complaints, a 3-tesla brain MRI, patient-reported outcomes (quality of life, fatigue, depression, anxiety, work performance), blood sampling and physical fitness. The MRI scans and blood sampling will be used to gain insight into underlying mechanisms. At 18 months online neuropsychological tests, self-reported cognitive complaints and patient-reported outcomes will be repeated.
Ethisc and dissemination: Study results may impact usual care if physical exercise improves cognitive functioning for breast cancer survivors.
Trial registration number: NTR6104.

Gepubliceerd: BMJ Open 2019 Jun 20;9(6):e028117
Impact factor: 2.376; Q2

Totale impact factor: 86.476
Gemiddelde impact factor: 3.603

Aantal artikelen 1e, 2e of laatste auteur: 5
Totale impact factor: 30.177
Gemiddelde impact factor: 6.035

Medische Microbiologie

1. Culture results from wound biopsy versus wound swab: does it matter for the assessment of wound infection?
Haalboom M, Blokhuis-Arkes MHE, Beuk RJ, Meerwaldt R, Klont R, Schijffelen MJ, Bowler PB, Burnet M, Sigl E, van der Palen JAM

Objectives: The aim of this study was to determine whether assessment of wound infection differs when culture results from wound biopsy versus wound swab are available in clinical practice.
Methods: For 180 eligible patients, a swab and biopsy were taken from one wound during a regular appointment at a wound care facility in eastern Netherlands. Culture results from both methods were supplemented with clinical information and provided to a panel of six experts who independently assessed each wound as infect or not, separately for swab and biopsy. Assessments for biopsy and swab were compared for the complete expert panel, and for individual experts.
Results: The complete expert panel provided the same wound assessment based on (clinical information and) culture results from wound biopsy and wound swab in 158 of 180 wounds (87.8%, kappa 0.67). For individual experts, agreement between biopsy and swab varied between 77% and 96%. However, there were substantial differences between experts: the same assessment was provided in 62 (34.4%) to 76 (42.2%) wounds for swab and biopsy respectively.
Conclusions: Assessment of infection does not significantly differ when culture results from swabs or biopsies are available. The substantial variability between individual experts indicates non-uniformity in the way wounds are assessed. This complicates accurate detection of infection and comparability between studies using assessment of infection as reference standard.

Gepubliceerd: Clin Microbiol Infect 2019;25(5):629.e7-629.e12
Impact factor: 6.425; Q1

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2. Changing epidemiology of meticillin-resistant Staphylococcus aureus in 42 hospitals in the Dutch-German border region, 2012 to 2016: results of the search-and-follow-policy
Jurke A, Daniels-Haardt I, Silvis W, Berends MS, Glasner C, Becker K, Kock R, Friedrich AW

Introduction: Meticillin-resistant Staphylococcus aureus (MRSA) is a major cause of healthcare-associated infections.AimWe describe MRSA colonisation/infection and bacteraemia rate trends in Dutch-German border region hospitals (NL-DE-BRH) in 2012-16.
Methods: All 42 NL-DE BRH (8 NL-BRH, 34 DE-BRH) within the cross-border network EurSafety Health-net provided surveillance data (on average ca 620,000 annual hospital admissions, of these 68.0% in Germany). Guidelines defining risk for MRSA colonisation/infection were reviewed. MRSA-related parameters and healthcare utilisation indicators were derived. Medians over the study period were compared between NL- and DE-BRH.

Results: Measures for MRSA cases were similar in both countries, however defining patients at risk for MRSA differed. The rate of nasopharyngeal MRSA screening swabs was 14 times higher in DE-BRH than in NL-BRH (42.3 vs 3.0/100 inpatients; p < 0.0001). The MRSA incidence was over seven times higher in DE-BRH than in NL-BRH (1.04 vs 0.14/100 inpatients; p < 0.0001). The nosocomial MRSA incidence-density was higher in DE-BRH than in NL-BRH (0.09 vs 0.03/1,000 patient days; p = 0.0002) and decreased significantly in DE-BRH (p = 0.0184) during the study. The rate of MRSA isolates from blood per 100,000 patient days was almost six times higher in DE-BRH than in NL-BRH (1.55 vs 0.26; p = 0.0041). The patients had longer hospital stays in DE-BRH than in NL-BRH (6.8 vs 4.9; p < 0.0001). DE-BRH catchment area inhabitants appeared to be more frequently hospitalised than their Dutch counterparts.
Conclusions: Ongoing IPC efforts allowed MRSA reduction in DE-BRH. Besides IPC, other local factors, including healthcare systems, could influence MRSA epidemiology.

Gepubliceerd: Euro Surveill 2019 Apr;24(15)
Impact factor: 7.421; Q1

Totale impact factor: 13.846
Gemiddelde impact factor: 6.923

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

Neurochirurgie

1. Between-hospital variation in mortality and survival after glioblastoma surgery in the Dutch Quality Registry for Neuro Surgery
De Witt Hamer PC, Ho VKY, Zwinderman AH, Ackermans L, Ardon H, Boomstra S, Bouwknegt W, van den Brink WA, Dirven CM, van der Gaag NA, van der Veer O, Idema AJS, Kloet A, Koopmans J, Ter Laan M, Verstegen MJT, Wagemakers M, Robe PAJT

Purpose: Standards for surgical decisions are unavailable, hence treatment decisions can be personalized, but also introduce variation in treatment and outcome. National registrations seek to monitor healthcare quality. The goal of the study is to measure between-hospital variation in risk-standardized survival outcome after glioblastoma surgery and to explore the association between survival and hospital characteristics in conjunction with patient-related risk factors.
Methods: Data of 2,409 adults with first-time glioblastoma surgery at 14 hospitals were obtained from a comprehensive, prospective population-based Quality Registry Neuro Surgery in The Netherlands between 2011 and 2014. We compared the observed survival with patient-specific risk-standardized expected early (30-day) mortality and late (2-year) survival, based on age, performance, and treatment year. We analyzed funnel plots, logistic regression and proportional hazards models.
Results: Overall 30-day mortality was 5.2% and overall 2-year survival was 13.5%. Median survival varied between 4.8 and 14.9 months among hospitals, and biopsy percentages ranged between 16 and 73%. One hospital had lower than expected early mortality, and four hospitals had lower than expected late survival. Higher case volume was related with lower early mortality (P = 0.031). Patient-related risk factors (lower age; better performance; more recent years of treatment) were significantly associated with longer overall survival. Of the hospital characteristics, longer overall survival was associated with lower biopsy percentage (HR 2.09, 1.34-3.26, P = 0.001), and not with academic setting, nor with case volume.
Conclusions: Hospitals vary more in late survival than early mortality after glioblastoma surgery. Widely varying biopsy percentages indicate treatment variation. Patient-related factors have a stronger association with overall survival than hospital-related factors.

Gepubliceerd: J Neurooncol 2019 Sep;144(2):313-23
Impact factor: 3.129; Q2

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2. A Parkinson's Disease Patient without Corpus Callosum
Kho KH, Leijten QH, Dorresteijn LDA

The authors report of a patient with Parkinson's disease in whom imaging revealed a complete agenesis of the corpus callosum. Although this co-occurrence is probably coincidental, this finding suggests that the bilateral degenerative changes in Parkinson's disease may occur independent of the interhemispheric connections.

Gepubliceerd: J Parkinsons Dis 2019;9(2):441-2
Impact factor: 3.698; Q2

3. Corticosteroid treatment compared with surgery in chronic subdural hematoma: a systematic review and meta-analysis
Holl DC, Volovici V, Dirven CMF, van Kooten F, Miah IP, Jellema K, Peul WC, van der Gaag NA, Kho KH, den Hertog HM, Dammers R, Lingsma HF

Background: There is an ongoing debate on the role of corticosteroids in the treatment of chronic subdural hematoma (CSDH). This study aims to evaluate the effectiveness of corticosteroids for the treatment of CSDH compared to surgery.
Method: A systematic search was performed in relevant databases up to January 2019 to identify RCTs or observational studies that compared at least two of three treatment modalities: the use of corticosteroids as a monotherapy (C), corticosteroids as an adjunct to surgery (CS), and surgery alone (S). Outcome measures were good neurological outcome, need for reintervention, mortality, and complications. Effect estimates were pooled and presented as relative risk (RR) with 95% confidence interval (95%CI).
Results: Of 796 initially identified studies, 7 were included in the meta-analysis. Risk of bias was generally high. There were no differences in good neurological outcome between treatment modalities. The need for reintervention varied between 4 and 58% in C, 4-12% in CS, and 7-26% in S. The need for reintervention was lower in CS compared with C (RR 3.34 [95% CI 1.53-7.29]; $p < 0.01$) and lower in CS compared with S (RR 0.44 [95% CI 0.27-0.72]; $p < 0.01$). Mortality varied between 0 and 4% in C, 0-13% in CS, and 0-44% in S. Mortality was lower in CS compared with S (RR 0.39 [95% CI 0.25-0.63]; $p < 0.01$). There were no differences in complications between treatment modalities.
Conclusions: This meta-analysis suggests that the addition of corticosteroids to surgery might be effective in the treatment of CSDH. However, the results must be interpreted with caution in light of the serious risk of bias of the included studies. This study stresses the need for large randomized trials to investigate the use of corticosteroids in the management of CSDH**.**

Gepubliceerd: Acta Neurochir (Wien) 2019 Jun;161(6):1231-42
Impact factor: 1.834; Q3

Totale impact factor: 8.661
Gemiddelde impact factor: 2.887

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 3.698
Gemiddelde impact factor: 3.698

Neurologie

1. Electroencephalographic reactivity as predictor of neurological outcome in postanoxic coma: A multicenter prospective cohort study
Admiraal MM, van Rootselaar AF, Hofmeijer J, Hoedemaekers CWE, van Kaam CR, Keijzer HM, van Putten MJAM, Schultz MJ, Horn J

Objective: Outcome prediction in patients after cardiac arrest (CA) is challenging. Electroencephalographic reactivity (EEG-R) might be a reliable predictor. We aimed to determine the prognostic value of EEG-R using a standardized assessment.
Methods: In a prospective cohort study, a strictly defined EEG-R assessment protocol was executed twice per day in adult patients after CA. EEG-R was classified as present or absent by 3 EEG readers, blinded to patient characteristics. Uncertain reactivity was classified as present. Primary outcome was best Cerebral Performance Category score (CPC) in 6 months after CA, dichotomized as good (CPC = 1-2) or poor (CPC = 3-5). EEG-R was considered reliable for predicting poor outcome if specificity was >/=95%. For good outcome prediction, a specificity of >/=80% was used. Added value of EEG-R was the increase in specificity when combined with EEG background, neurological examination, and somatosensory evoked potentials (SSEPs).
Results: Of 160 patients enrolled, 149 were available for analyses. Absence of EEG-R for poor outcome prediction had a specificity of 82% and a sensitivity of 73%. For good outcome prediction, specificity was 73% and sensitivity 82%. Specificity for poor outcome prediction increased from 98% to 99% when EEG-R was added to a multimodal model. For good outcome prediction, specificity increased from 70% to 89%.
Interpretation: EEG-R testing in itself is not sufficiently reliable for outcome prediction in patients after CA. For poor outcome prediction, it has no substantial added value to EEG background, neurological examination, and SSEPs. For prediction of good outcome, EEG-R seems to have added value**.**

Gepubliceerd: Ann Neurol 2019 Jul;86(1):17-27
Impact factor: 9.496; Q1

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2. Glucose Modifies the Effect of Endovascular Thrombectomy in Patients With Acute Stroke
Chamorro A, Brown S, Amaro S, Hill MD, Muir KW, Dippel DWJ, van Zwam W, Butcher K, Ford GA, den Hertog HM, Mitchell PJ, Demchuk AM, Majoie CBLM, Bracard S, Sibon I, Jadhav AP, Lara-Rodriguez B, van der Lugt A, Osei E, Renu A, Richard S, Rodriguez-Luna D, Donnan GA, Dixit A, Almekhlafi M, Deltour S, Epstein J, Guillon B, Bakchine S, Gomis M, du Mesnil de RR, Lopes D, Reddy V, Rudel G, Roos YBWE, Bonafe A, Diener HC, Berkhemer OA, Cloud GC, Davis SM, van OR, Guillemin F, Goyal M, Campbell BCV, Menon BK

Background and Purpose: Hyperglycemia is a negative prognostic factor after acute ischemic stroke but is not known whether glucose is associated with the effects of endovascular thrombectomy (EVT) in patients with large-vessel stroke. In a pooled-

data meta-analysis, we analyzed whether serum glucose is a treatment modifier of the efficacy of EVT in acute stroke.
Methods: Seven randomized trials compared EVT with standard care between 2010 and 2017 (HERMES Collaboration [highly effective reperfusion using multiple endovascular devices]). One thousand seven hundred and sixty-four patients with large-vessel stroke were allocated to EVT (n=871) or standard care (n=893). Measurements included blood glucose on admission and functional outcome (modified Rankin Scale range, 0-6; lower scores indicating less disability) at 3 months. The primary analysis evaluated whether glucose modified the effect of EVT over standard care on functional outcome, using ordinal logistic regression to test the interaction between treatment and glucose level.
Results: Median (interquartile range) serum glucose on admission was 120 (104-140) mg/dL (6.6 mmol/L [5.7-7.7] mmol/L). EVT was better than standard care in the overall pooled-data analysis adjusted common odds ratio (acOR), 2.00 (95% CI, 1.69-2.38); however, lower glucose levels were associated with greater effects of EVT over standard care. The interaction was nonlinear such that significant interactions were found in subgroups of patients split at glucose < or >90 mg/dL (5.0 mmol/L; P=0.019 for interaction; acOR, 3.81; 95% CI, 1.73-8.41 for patients < 90 mg/dL versus 1.83; 95% CI, 1.53-2.19 for patients >90 mg/dL), and glucose < or >100 mg/dL (5.5 mmol/L; P=0.004 for interaction; acOR, 3.17; 95% CI, 2.04-4.93 versus acOR, 1.72; 95% CI, 1.42-2.08) but not between subgroups above these levels of glucose.
Conclusions: EVT improved stroke outcomes compared with standard treatment regardless of glucose levels, but the treatment effects were larger at lower glucose levels, with significant interaction effects persisting up to 90 to 100 mg/dL (5.0-5.5 mmol/L). Whether tight control of glucose improves the efficacy of EVT after large-vessel stroke warrants appropriate testing**.**

Gepubliceerd: Stroke 2019 Mar;50(3):690-6
Impact factor: 6.058;Q1

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3. Infraslow activity as a potential modulator of corticomotor excitability
de Goede AA, van Putten MJAM

Fluctuations in cortical excitability are a candidate mechanism involved in the trial-to-trial variation of motor evoked potentials (MEPs) to transcranial magnetic stimulation (TMS). We explore whether infraslow EEG activity (<0.1 Hz) modulates corticomotor excitability by evaluating the presence of temporal and phase clustering of TMS-induced MEPs. In addition, we evaluate the dependence of MEP amplitude on the phase of the infraslow activity. Twenty-three subjects were stimulated at an intensity above the resting motor threshold (rMT) and ten at the rMT. We evaluated whether temporal and phase clustering of MEP size and MEP generation were present, using 1,000 surrogates with a similar amplitude or occurrence distribution. To evaluate the MEP amplitude dependence, we used the least-square method to approximate the linear circular data by fitting a sine function. We observed significant temporal clustering at a group level, in all individual subjects stimulated at rMT and in the majority of those stimulated above rMT, suggesting underlying determinism of corticomotor excitability instead of randomly generated fluctuations. The majority of subjects showed significant phase clustering for MEP size and for MEP occurrence, and significant phase clustering was found at the group level. Furthermore, in

approximately one-quarter to one-half of the subjects we found a significant correlation and dependence of MEP amplitude on the phase of infraslow activity, respectively. Although other mechanisms very likely contribute as well, our findings seem to suggest that infraslow activity is involved in the variability of cortical excitability and TMS-induced responses. **New & noteworthy**: Cortical excitability measures are highly variable during transcranial magnetic stimulation. Although ongoing brain oscillations are assumed to modulate excitability, no consistent associations are found for the traditional frequency bands. We focus on the role of infraslow EEG activity, defined as rhythms with frequencies < 0.1 Hz. We provide experimental evidence suggesting that infraslow activity most likely modulates corticomotor excitability and that response variation could be reduced when stimulation is targeted at a specific infraslow phase**.**

Gepubliceerd: J Neurophysiol 2019 Jul 1;122(1):325-35
Impact factor: 2.614; Q2

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4. Association between somatosensory evoked potentials and EEG in comatose patients after cardiac arrest
Glimmerveen AB, Ruijter BJ, Keijzer HM, Tjepkema-Cloostermans MC, van Putten MJAM, Hofmeijer J

Objective: To analyze the association between SSEP results and EEG results in comatose patients after cardiac arrest, including the added value of repeated SSEP measurements.
Methods: Continuous EEG was measured in 619 patients during the first 3-5days after cardiac arrest. SSEPs were recorded daily in the first 55 patients, and on indication in later patients. EEGs were visually classified at 12, 24, 48, and 72h after cardiac arrest, and at the time of SSEP. Outcome at 6m was dichotomized as good (Cerebral Performance Category 1-2) or poor (CPC 3-5). SSEP and EEG results were related to outcome. Additionally, SSEP results were related to the EEG patterns at the time of SSEP.
Results: Absent SSEP responses and suppressed or synchronous EEG on suppressed background >/=24h after cardiac arrest were invariably associated with poor outcome. SSEP and EEG identified different patients with poor outcome (joint sensitivity 39% at specificity 100%). N20 responses were always preserved in continuous traces at >8Hz. Absent SSEPs did not re-emerge during the first five days.
Conclusions: SSEP and EEG results may diverge after cardiac arrest.
Significance: SSEP and EEG together identify more patients without chance of recovery than one of these alone**.**

Gepubliceerd: Clin Neurophysiol 2019 Nov;130(11):2026-31
Impact factor: 3.675; Q2

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5. An abnormal CT scan following a mild traumatic brain injury; what then?
Hageman G, Nihom J

CT scan reveals traumatic intracranial abnormalities in fewer than 10% of patients following mild traumatic brain injury (mTBI). Management policy in these patients is not clear. Clinical or radiological deterioration occurs in 10-20% of this risk group, usually within 24 hours and often without neurosurgical consequences. Patients with mTBI and subarachnoid blood or small foci of contusion do not need to be admitted to medium/high care or to the ICU. This is warranted in patients fulfilling the following criteria: age > 65 years; a Glasgow Coma Scale (GCS) score < 15; anticoagulant use; or multiple trauma. It is also warranted by fulfilment of one or more of the following CT-criteria: shift of the midline; subdural or epidural haematoma; a temporal or subfrontal focus of contusion; or intraparenchymatous bleeding > 10 ml. Repeated CT-scan is only indicated in case of clinical deterioration. Transfer to a neurosurgical centre is not necessary in the majority of patients with mTBI and CT abnormalities**.**

Gepubliceerd: Ned Tijdschr Geneeskd 2019 Oct 29;163
Impact factor: 0; nvt

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6. A randomized controlled efficacy study of the Medido medication dispenser in Parkinson's disease

Hannink K, Ter Brake L, Oonk NGM, Wertenbroek AA, Piek M, Vree-Egberts L, Faber MJ, van der Palen J, Dorresteijn LD

Background: Complex medication schedules in Parkinson's disease (PD) result in lower therapy adherence, which contributes to suboptimal therapy and clinical deterioration. Medication reminder systems might improve therapy adherence and subsequently improve symptoms of PD. This randomized controlled study assessed the effect of the electronic medication dispenser Medido on physical disability in PD, as a proxy for changes in therapy adherence.x
Methods: Eighty-seven patients were randomized into the Medido group or control group. The primary outcome of physical disability was measured by the AMC Linear Disability Scale (ALDS). Secondary outcomes were quality of life (QoL) (PDQ-39), health status (EQ5D-5L, VAS), non-motor symptoms (NMS-Quest), and QoL of the caregiver (PDQ-carer). Measurements were performed at baseline, and after 3 and 6 months follow-up.
Results: When using the Medido, a non-significant improvement of 3.0 points (95% CI -5.6;11.6) was seen in ALDS. The exploratory subgroup Hoehn & Yahr classification (H&Y) > 2.5 improved significantly on ALDS with 14.7 points (95% CI -28.5;-0.9, p = 0.029 for group x time interaction). QoL deteriorated with 1.0 point in PDQ-39 (p = 0.01 for group x time interaction) in favor of the control group. Non-significant differences were observed for VAS (0.4 points, p = 0.057) and NMS-Quest (1.3 points, p = 0.095) in favor of the Medido group. No changes over time were observed in EQ5D-5L and PDQ-carer.
Conclusions: Based on these data, no firm conclusion can be drawn, but use of the Medido medication dispenser may result in a clinical improvement of physical disability and seems particularly appropriate for more severe patients.
Trial registration: NTR3917 Registered 19 March 2013**.**

Gepubliceerd: BMC Geriatr 2019 Oct 16;19(1):273
Impact factor: 2.818; Q1

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7. Severely Disturbed Sleep in Patients With Acute Ischemic Stroke on Stroke Units: A Pilot Study
Hofmeijer J, van Kaam R, Vermeer SE, van Putten MJAM

Introduction: Previous studies revealed a high prevalence of sleep-wake disturbances in subacute and chronic stroke. We analyzed sleep quantity and quality in patients with hyperacute ischemic stroke on stroke units.
Methods: We categorized sleep stages as N1, N2, N3, and REM according to the 2017 criteria of the American Academy of Sleep Medicine in 23 continuous, overnight EEG registrations from 18 patients, starting within 48 h since the onset of cortical ischemic stroke. Associations between presence and duration of sleep stages, and secondary deterioration or functional outcome were analyzed.
Results: Physiological sleep cycles were seen in none of the patients. Otherwise, sleep stages alternated chaotically, both during day- and during nighttime, with a sleep efficiency of 30% and 10.5 +/- 4.4 (mean +/- SD) awakenings per hour of sleep. We cannot differentiate between stroke related and external factors. Only few interruptions could be related to planned nightly wake up calls, but turbulence on stroke units may have played a role. Six patients (seven nights) did not reach deep sleep (N3), 10 patients (13 nights) did not reach REM sleep. If reached, the mean durations of deep and REM sleep were short, with 37 (standard deviation (SD) 25) and 18 (SD15) minutes, respectively. Patients with secondary deterioration more often lacked deep sleep (N3) than patients without secondary deterioration [4 (57%) vs. 2 (25%)], but without statistical significance (p = 0.12).
Conclusion: We show that sleep is severely disturbed in patients with acute ischemic stroke admitted to stroke units. Larger studies are needed to clarify associations between deprivation of deep sleep and secondary deterioration**.**

Gepubliceerd: Front Neurol 2019;10:1109
Impact factor: 2.635; Q3

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8. Corticosteroid treatment compared with surgery in chronic subdural hematoma: a systematic review and meta-analysis
Holl DC, Volovici V, Dirven CMF, van Kooten F, Miah IP, Jellema K, Peul WC, van der Gaag NA, Kho KH, den Hertog HM, Dammers R, Lingsma HF

Background: There is an ongoing debate on the role of corticosteroids in the treatment of chronic subdural hematoma (CSDH). This study aims to evaluate the effectiveness of corticosteroids for the treatment of CSDH compared to surgery.
Method: A systematic search was performed in relevant databases up to January 2019 to identify RCTs or observational studies that compared at least two of three treatment modalities: the use of corticosteroids as a monotherapy (C), corticosteroids as an adjunct to surgery (CS), and surgery alone (S). Outcome measures were good neurological outcome, need for reintervention, mortality, and complications. Effect estimates were pooled and presented as relative risk (RR) with 95% confidence interval (95%CI).
Results: Of 796 initially identified studies, 7 were included in the meta-analysis. Risk of bias was generally high. There were no differences in good neurological outcome between treatment modalities. The need for reintervention varied between 4 and 58%

in C, 4-12% in CS, and 7-26% in S. The need for reintervention was lower in CS compared with C (RR 3.34 [95% CI 1.53-7.29]; p < 0.01) and lower in CS compared with S (RR 0.44 [95% CI 0.27-0.72]; p < 0.01). Mortality varied between 0 and 4% in C, 0-13% in CS, and 0-44% in S. Mortality was lower in CS compared with S (RR 0.39 [95% CI 0.25-0.63]; p < 0.01). There were no differences in complications between treatment modalities.
Conclusions: This meta-analysis suggests that the addition of corticosteroids to surgery might be effective in the treatment of CSDH. However, the results must be interpreted with caution in light of the serious risk of bias of the included studies. This study stresses the need for large randomized trials to investigate the use of corticosteroids in the management of CSDH**.**

Gepubliceerd: Acta Neurochir (Wien) 2019 Jun;161(6):1231-42
Impact factor: 1.834; Q3

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9. Validation of the Auditory Stroop Task to increase cognitive load in walking tasks in healthy elderly and persons with Parkinson's disease
Janssen S, Heijs JJA, van der Meijs W, Nonnekes J, Bittner M, Dorresteijn LDA, Bloem BR, van Wezel RJA, Heida T

Background: The development of treatments for freezing of gait (FOG) in Parkinson's disease (PD) requires experimental study set-ups in which FOG is likely to occur, and is amenable to therapeutic interventions. We explore whether the 'Auditory Stroop Task' (AST) can be used to increase cognitive load (and thereby elicit FOG), simultaneously with visual cues (as a therapeutic intervention for FOG). We additionally examined how these two contrasting effects might interact in affecting gait and FOG parameters.
Objectives: We investigated whether: (1) the 'Auditory Stroop Task' (AST) influences gait in healthy elderly and persons with PD who experience FOG, and increases the frequency of FOG events among PD patients; (2) the AST and visual cues interact; and (3) different versions of the AST exert different cognitive loads.
Methods: In 'Experiment 1', 19 healthy elderly subjects performed a walking task while performing a high and low load version of the AST. Walking with a random numbers task, and walking without cognitive load served as control conditions. In 'Experiment 2', 20 PD patients with FOG and 18 healthy controls performed a walking task with the AST, and no additional cognitive load as control condition. Both experiments were performed with and without visual cues. Velocity, cadence, stride length, and stride time were measured in all subjects. FOG severity was measured in patients.
Results: Compared to the control conditions, the AST negatively affected all gait parameters in both patients and controls. The AST did not increase the occurrence of FOG in patients. Visual cues reduced the decline in stride length induced by cognitive load in both groups. Both versions of the AST exerted similar effects on gait parameters in controls.
Conclusions: The AST is well-suited to simulate the effects of cognitive load on gait parameters, but not FOG severity, in gait experiments in persons with PD and FOG**.**

Gepubliceerd: PLoS One 2019;14(8):e0220735
Impact factor: 2.776; Q2

10. A Parkinson's Disease Patient without Corpus Callosum
Kho KH, Leijten QH, Dorresteijn LDA

The authors report of a patient with Parkinson's disease in whom imaging revealed a complete agenesis of the corpus callosum. Although this co-occurrence is probably coincidental, this finding suggests that the bilateral degenerative changes in Parkinson's disease may occur independent of the interhemispheric connections**.**

Gepubliceerd: J Parkinsons Dis 2019;9(2):441-2
Impact factor: 3.698; Q2

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11. Clinical prediction of thrombectomy eligibility: A systematic review and 4-item decision tree
Koster GT, Nguyen TTM, van Zwet EW, Garcia BL, Rowling HR, Bosch J, Schonewille WJ, Velthuis BK, van den Wijngaard IR, den Hertog HM, Roos YB, van Walderveen MA, Wermer MJ, Kruyt ND

Background: A clinical large anterior vessel occlusion (LAVO)-prediction scale could reduce treatment delays by allocating intra-arterial thrombectomy (IAT)-eligible patients directly to a comprehensive stroke center. AIM: To subtract, validate and compare existing LAVO-prediction scales, and develop a straightforward decision support tool to assess IAT-eligibility.
Methods: We performed a systematic literature search to identify LAVO-prediction scales. Performance was compared in a prospective, multicenter validation cohort of the Dutch acute Stroke study (DUST) by calculating area under the receiver operating curves (AUROC). With group lasso regression analysis, we constructed a prediction model, incorporating patient characteristics next to National Institutes of Health Stroke Scale (NIHSS) items. Finally, we developed a decision tree algorithm based on dichotomized NIHSS items.
Results: We identified seven LAVO-prediction scales. From DUST, 1316 patients (35.8% LAVO-rate) from 14 centers were available for validation. FAST-ED and RACE had the highest AUROC (both >0.81, $p < 0.01$ for comparison with other scales). Group lasso analysis revealed a LAVO-prediction model containing seven NIHSS items (AUROC 0.84). With the GACE (Gaze, facial Asymmetry, level of Consciousness, Extinction/inattention) decision tree, LAVO is predicted (AUROC 0.76) for 61% of patients with assessment of only two dichotomized NIHSS items, and for all patients with four items.
Conclusion: External validation of seven LAVO-prediction scales showed AUROCs between 0.75 and 0.83. Most scales, however, appear too complex for Emergency Medical Services use with prehospital validation generally lacking. GACE is the first LAVO-prediction scale using a simple decision tree as such increasing feasibility, while maintaining high accuracy. Prehospital prospective validation is planned**.**

Gepubliceerd: Int J Stroke 2019 Jul;14(5):530-9
Impact factor: 4.466; Q1

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12. Mild stimulation improves neuronal survival in an in-vitro model of the ischemic penumbra
Muzzi L, Hassink G, Levers M, Jansman M, Frega M, Hofmeijer J, van Putten MJAM, le Feber J

Objective: In the core of a brain infarct, characterized by severely reduced blood supply, loss of neuronal function is rapidly followed by neuronal death. In peripheral areas of the infarct, the penumbra, damage is initially reversible, and neuronal activity is typically reduced due to ischemia-induced synaptic failure. There is limited understanding of factors governing neuronal recovery or the transition to irreversible damage. Neuronal activity has been shown to be crucial for survival. Consequently, hypoxia induced neuronal inactivity may contribute to cell death, and activation of penumbral neurons possibly improves survival. Adversely, activation increases ATP demand, and a balance should be found between the available energy and sufficient activity.
Approach: We monitored activity and viability of neurons in an in vitro model of the penumbra, consisting of (rat) neuronal networks on micro electrode arrays (MEAs) under controlled hypoxic conditions. We tested effects of optogenetic and electrical activation during hypoxia.
Main results: Mild stimulation yielded significantly better recovery of activity immediately after re-oxygenation, compared with no stimulation, and a 60-70% higher survival rate after 5 days. Stronger stimulation was not associated with better recovery than no stimulation, suggesting that beneficial effects depend on a delicate balance between sufficient activity and available energy.
Significance: We show that mild activation during hypoxia/ischemia is beneficial for cell survival in an in vitro model of the penumbra. This finding opposes the current common belief that suppression of neuronal activity is the cornerstone of neuroprotection during cerebral ischemia, and may open new possibilities for the treatment of secondary brain damage after stroke**.**

Gepubliceerd: J Neural Eng 2019 Oct 28;17(1):016001
Impact factor: 4.551; Q1

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13. The effect of a structured medication review on quality of life in Parkinson's disease: The study protocol
Oonk NGM, Movig KLL, Munster EM, Koehorst-Ter Huurne K, van der Palen J, Dorresteijn LDA

Background: Treatment of Parkinson's disease (PD) is symptomatic and frequently consists of complicated medication regimes. This negatively influences therapy adherence, resulting in lower benefit of treatment, drug related problems and decreased quality of life (QoL). A potential effective intervention strategy is a structured medication review, executed by community pharmacists. However, little is known about the effects on clinical endpoints like QoL, as well as on feasibility and cost-effectiveness in PD patients.
Objectives: To assess the effect of a structured medication review on QoL in PD patients. Secondary objectives are measurements of physical disability, activities in daily life, non-motor symptoms, health state, personal carers' QoL and cost-

effectiveness. Furthermore, a better insight in the process of performing medication reviews will be obtained from the perspective of community pharmacists.
Methods: In this multicenter randomized controlled trial we aim to enroll 200 PD patients from the outpatient clinic of three Dutch hospitals. Community pharmacists will perform a structured medication review in half of the assigned patients; the other half will receive usual care. Data obtained by use of six validated questionnaires will be collected at baseline and after 3 and 6 months of follow-up. Semi-structured interviews with community pharmacists will be conducted till data saturation has been reached.
Discussion: This trial targets a high-risk patient group for whom optimizing therapy by a structured medication review might be of added value. If effectiveness is proven, this could further promote the implementation of pharmaceutical care in a primary care setting**.**

Gepubliceerd: Contemp Clin Trials Commun 2019 Mar;13:100308
Impact factor: 0; nvt

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14. Clinical and genetic characteristics of late-onset Huntington's disease
Oosterloo M, Bijlsma EK, van Kuijk SM, Minkels F, de Die-Smulders CE, REGISTRY Investigators of the European Huntington's Disease Network, includes van Hout M and van Vugt JPP

Background: The frequency of late-onset Huntington's disease (>59 years) is assumed to be low and the clinical course milder. However, previous literature on late-onset disease is scarce and inconclusive.
Objective: Our aim is to study clinical characteristics of late-onset compared to common-onset HD patients in a large cohort of HD patients from the Registry database.
Methods: Participants with late- and common-onset (30-50 years)were compared for first clinical symptoms, disease progression, CAG repeat size and family history. Participants with a missing CAG repeat size, a repeat size of </=35 or a UHDRS motor score of </=5 were excluded.
Results: Of 6007 eligible participants, 687 had late-onset (11.4%) and 3216 (53.5%) common-onset HD. Late-onset (n=577) had significantly more gait and balance problems as first symptom compared to common-onset (n=2408) (P<.001). Overall motor and cognitive performance (P<.001) were worse, however only disease motor progression was slower (coefficient, -0.58; SE 0.16; P<.001) compared to the common-onset group. Repeat size was significantly lower in the late-onset (n=40.8; SD 1.6) compared to common-onset (n=44.4; SD 2.8) (P<.001). Fewer late-onset patients (n=451) had a positive family history compared to common-onset (n=2940) (P<.001).
Conclusions: Late-onset patients present more frequently with gait and balance problems as first symptom, and disease progression is not milder compared to common-onset HD patients apart from motor progression. The family history is likely to be negative, which might make diagnosing HD more difficult in this population. However, the balance and gait problems might be helpful in diagnosing HD in elderly patients**.**

Gepubliceerd: Parkinsonism Relat Disord 2019;61:101-5

Impact factor: 4.360; Q1

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15. Early electroencephalography for outcome prediction of postanoxic coma: A prospective cohort study
Ruijter BJ, Tjepkema-Cloostermans MC, Tromp SC, van den Bergh WM, Foudraine NA, Kornips FHM, Drost G, Scholten E, Bosch FH, Beishuizen A, van Putten MJAM, Hofmeijer J

Objective: To provide evidence that early electroencephalography (EEG) allows for reliable prediction of poor or good outcome after cardiac arrest.
Methods: In a 5-center prospective cohort study, we included consecutive, comatose survivors of cardiac arrest. Continuous EEG recordings were started as soon as possible and continued up to 5 days. Five-minute EEG epochs were assessed by 2 reviewers, independently, at 8 predefined time points from 6 hours to 5 days after cardiac arrest, blinded for patients' actual condition, treatment, and outcome. EEG patterns were categorized as generalized suppression (<10 muV), synchronous patterns with >/=50% suppression, continuous, or other. Outcome at 6 months was categorized as good (Cerebral Performance Category [CPC] = 1-2) or poor (CPC = 3-5).
Results: We included 850 patients, of whom 46% had a good outcome. Generalized suppression and synchronous patterns with >/=50% suppression predicted poor outcome without false positives at >/=6 hours after cardiac arrest. Their summed sensitivity was 0.47 (95% confidence interval [CI] = 0.42-0.51) at 12 hours and 0.30 (95% CI = 0.26-0.33) at 24 hours after cardiac arrest, with specificity of 1.00 (95% CI = 0.99-1.00) at both time points. At 36 hours or later, sensitivity for poor outcome was </=0.22. Continuous EEG patterns at 12 hours predicted good outcome, with sensitivity of 0.50 (95% CI = 0.46-0.55) and specificity of 0.91 (95% CI = 0.88-0.93); at 24 hours or later, specificity for the prediction of good outcome was <0.90.
Interpretation: EEG allows for reliable prediction of poor outcome after cardiac arrest, with maximum sensitivity in the first 24 hours. Continuous EEG patterns at 12 hours after cardiac arrest are associated with good recovery. ANN NEUROL 2019;86:203-214**.**

Gepubliceerd: Ann Neurol 2019 Aug;86(2):203-14
Impact factor: 9.496; Q1

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16. Propofol does not affect the reliability of early EEG for outcome prediction of comatose patients after cardiac arrest
Ruijter BJ, van Putten MJAM, van den Bergh WM, Tromp SC, Hofmeijer J

Objective: To quantify the effects of propofol on the EEG after cardiac arrest and to assess their influence on predictions of outcome.
Methods: In a prospective multicenter cohort study, we analyzed EEG recordings within the first 72h after cardiac arrest. At six time points, EEGs were classified as favorable (continuous background), unfavorable (generalized suppression or synchronous patterns with >/=50% suppression), or intermediate. Quantitative EEG included measures for amplitude, background continuity, dominant frequency, and

burst-suppression amplitude ratio (BSAR). The effect of propofol on each measure was estimated using mixed effects regression.
Results: We included 496 patients. The EEG after propofol cessation had no additional value over EEG-based outcome predictions during propofol administration at 12h after cardiac arrest. Propofol was associated with decreased EEG amplitude, background continuity and dominant frequency, and increased BSAR. However, propofol did neither increase the chance of unfavorable EEG patterns (adjusted odds ratio (aOR) 0.95 per increase of 2mg/kg/h, 95%-CI: 0.81-1.11) nor decrease the chance of favorable EEG patterns (aOR 0.98, 95%-CI: 0.89-1.09).
Conclusions: Propofol induces changes of the postanoxic EEG, but does not affect its value for the prediction of outcome. SIGNIFICANCE: We confirm the reliability of EEG-based outcome predictions in propofol-sedated patients after cardiac arrest**.**

Gepubliceerd: Clin Neurophysiol 2019 Aug;130(8):1263-70
Impact factor: 3.675; Q2

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17. Simulating perinodal changes observed in immune-mediated neuropathies: impact on conduction in a model of myelinated motor and sensory axons
Sleutjes BTHM, Kovalchuk MO, Durmus N, Buitenweg JR, van Putten MJAM, van den Berg LH, Franssen H

Immune-mediated neuropathies affect myelinated axons, resulting in conduction slowing or block that may affect motor and sensory axons differently. The underlying mechanisms of these neuropathies are not well understood. Using a myelinated axon model, we studied the impact of perinodal changes on conduction. We extended a longitudinal axon model (41 nodes of Ranvier) with biophysical properties unique to human myelinated motor and sensory axons. We simulated effects of temperature and axonal diameter on conduction and strength-duration properties. We then studied effects of impaired nodal sodium channel conductance and paranodal myelin detachment by reducing periaxonal resistance, as well as their interaction, on conduction in the 9 middle nodes and enclosed paranodes. Finally, we assessed the impact of reducing the affected region (5 nodes) and adding nodal widening. Physiological motor and sensory conduction velocities and changes to axonal diameter and temperature were observed. The sensory axon had a longer strength-duration time constant. Reducing sodium channel conductance and paranodal periaxonal resistance induced progressive conduction slowing. In motor axons, conduction block occurred with a 4-fold drop in sodium channel conductance or a 7.7-fold drop in periaxonal resistance. In sensory axons, block arose with a 4.8-fold drop in sodium channel conductance or a 9-fold drop in periaxonal resistance. This indicated that motor axons are more vulnerable to developing block. A boundary of block emerged when the two mechanisms interacted. This boundary shifted in opposite directions for a smaller affected region and nodal widening. These differences may contribute to the predominance of motor deficits observed in some immune-mediated neuropathies.NEW & NOTEWORTHY Immune-mediated neuropathies may affect myelinated motor and sensory axons differently. By the development of a computational model, we quantitatively studied the impact of perinodal changes on conduction in motor and sensory axons. Simulations of increasing nodal sodium channel dysfunction and paranodal myelin detachment induced progressive conduction slowing. Sensory axons were more resistant to block

than motor axons. This could explain the greater predisposition of motor axons to functional deficits observed in some immune-mediated neuropathies**.**

Gepubliceerd: J Neurophysiol 2019 Sep 1;122(3):1036-49
Impact factor: 2.614; Q2

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18. Resting Motor Threshold, MEP and TEP Variability During Daytime
Ter Braack EM, de Goede AA, van Putten MJAM

Humans show a variation in physiological processes during the day. To reliably assess (changes in) cortical excitability with transcranial magnetic stimulation (TMS), it is relevant to know the natural variation in TMS readouts during the day. In case of significant daytime variations, this should be taken into account when scheduling (follow-up) measurements. This study aims to evaluate the influence of the time of day on the resting motor threshold (RMT), motor evoked potential (MEP) and TMS evoked potential (TEP) in healthy controls. TMS-EMG-EEG was recorded in 16 healthy subjects. At both motor cortices, we administered 75 pulses at an intensity of 110% RMT. Subjects were stimulated during five sessions in one day (8:00 AM, 10:30 AM, 1:00 PM, 3:30 PM and 6:00 PM) while keeping the stimulation intensity constant. We compared the TEP waveforms between the five sessions with a cluster-based permutation analysis, and the RMT and MEP amplitude with rmANOVA. In general there were no significant differences between the five sessions in the RMT, MEP amplitude or TEP. Only for the left side, N100 amplitude was larger at 3:30 PM than 10:30 AM. The standard deviation of the P30 and N100 amplitude was significantly higher between subjects within one session than within single subjects during the day. The TEP is highly reproducible during the day, with a low intra-individual variation compared to the inter-individual variation. In addition, we found no significant variation of the RMT and MEP amplitude between multiple sessions on one day**.**

Gepubliceerd: Brain Topogr 2019;32(1):17-27
Impact factor: 3.104; Q2

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19. Outcome Prediction in Postanoxic Coma With Deep Learning
Tjepkema-Cloostermans MC, da Silva Lourenco C, Ruijter BJ, Tromp SC, Drost G, Kornips FHM, Beishuizen A, Bosch FH, Hofmeijer J, van Putten MJAM

Objectives: Visual assessment of the electroencephalogram by experienced clinical neurophysiologists allows reliable outcome prediction of approximately half of all comatose patients after cardiac arrest. Deep neural networks hold promise to achieve similar or even better performance, being more objective and consistent.
Design: Prospective cohort study.
Setting: Medical ICU of five teaching hospitals in the Netherlands.
Patients: Eight-hundred ninety-five consecutive comatose patients after cardiac arrest.
Interventions: None.
Measurements and main results: Continuous electroencephalogram was recorded during the first 3 days after cardiac arrest. Functional outcome at 6 months was

classified as good (Cerebral Performance Category 1-2) or poor (Cerebral Performance Category 3-5). We trained a convolutional neural network, with a VGG architecture (introduced by the Oxford Visual Geometry Group), to predict neurologic outcome at 12 and 24 hours after cardiac arrest using electroencephalogram epochs and outcome labels as inputs. Output of the network was the probability of good outcome. Data from two hospitals were used for training and internal validation (n = 661). Eighty percent of these data was used for training and cross-validation, the remaining 20% for independent internal validation. Data from the other three hospitals were used for external validation (n = 234). Prediction of poor outcome was most accurate at 12 hours, with a sensitivity in the external validation set of 58% (95% CI, 51-65%) at false positive rate of 0% (CI, 0-7%). Good outcome could be predicted at 12 hours with a sensitivity of 48% (CI, 45-51%) at a false positive rate of 5% (CI, 0-15%) in the external validation set.
Conclusions: Deep learning of electroencephalogram signals outperforms any previously reported outcome predictor of coma after cardiac arrest, including visual electroencephalogram assessment by trained electroencephalogram experts. Our approach offers the potential for objective and real time, bedside insight in the neurologic prognosis of comatose patients after cardiac arrest**.**

Gepubliceerd: Crit Care Med 2019 Oct;47(10):1424-32
Impact factor: 6.971; Q1

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20. Comparison of outcome in stroke patients admitted during working hours vs. off-hours; a single-center cohort study
Tuinman MP, van Golde EGA, Portier RP, Knottnerus ILH, van der Palen J, den Hertog HM, Brouwers PJAM

Introduction: We aimed to disprove an in-hospital off-hour effect in stroke patients by adjusting for disease severity and poor prognostic findings on imaging.
Patient and methods: Our study included 5378 patients from a single center prospective stroke registry of a large teaching hospital in the Netherlands, admitted between January 2003 and June 2015. Patients were categorized by admission time, off-hours (OH) or working hours (WH). The in-hospital mortality, 7-day mortality, unfavorable functional outcome (modified Rankin scale > 2) and discharge to home were analyzed. Results were adjusted for age, sex, stroke severity (NIHSS score) and unfavorable findings on imaging of the brain (midline shift and dense vessel sign).
Results: Overall, 2796 patients (52%) were admitted during OH, which had a higher NIHSS score [3 (IQR 2-8) vs. 3 (IQR 2-6): $p < 0.01$] and had more often a dense vessel sign at admission (7.9% vs. 5.4%: $p < 0.01$). There was no difference in mortality between the OH-group and WH-group (6.2% vs. 6.0%; $p = 0.87$). The adjusted hazard ratio of in-hospital mortality during OH was 0.87 (95% CI: 0.70-1.08). Analysis of 7-day mortality showed similar results. Unadjusted, the OH-group had an unfavorable outcome [OR: 1.14 (95% CI: 1.02-1.27)] and could less frequently be discharged to home [OR: 1.16 (95% CI: 1.04-1.29)], which was no longer present after adjustment. DISCUSSION AND
Conclusions: The overall outcome of stroke patients admitted to a large Dutch teaching hospital is not influenced by time of admission. When studying OH effects,

adjustment for disease severity and poor prognostic findings on imaging is crucial before drawing conclusions on staffing and material**.**

Gepubliceerd: J Neurol 2019;266(3):782-9
Impact factor: 4.204; Q1

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21. Normalization of EEG in depression after antidepressant treatment with sertraline? A preliminary report
van der Vinne N, Vollebregt MA, Boutros NN, Fallahpour K, van Putten MJAM, Arns M

Background: MDD patients with abnormal EEG patterns seem more likely to be non-responsive to the antidepressants escitalopram and venlafaxine, but not sertraline, than patients without EEG abnormalities. This finding suggests that patients with both MDD and abnormal EEGs may differentially respond to antidepressant treatment. In the current study, we investigated whether depressed patients with an abnormal EEG show a normalization of the EEG related to antidepressant treatment and response and whether such effect is drug specific, and whether having had early life stress (ELS) increases the chance of abnormal activity.
Methods: Baseline and week 8 EEGs and depression symptoms were extracted from a large multicenter study (iSPOT-D, n=1008) where depressed patients were randomized to escitalopram, sertraline, or venlafaxine-XR treatment. We calculated Odds Ratios of EEG normalization and depression response in patients with an abnormal EEG at baseline, comparing sertraline versus other antidepressants.
Results: Fifty seven patients with abnormal EEGs were included. EEGs did not normalize significantly more with sertraline compared to other antidepressants (OR = 1.9, p = .280). However, patients with a normalized EEG taking sertraline were 5.2 times more likely to respond than subjects taking other antidepressants (p = .019). ELS was not significantly related to abnormal activity. LIMITATIONS: Neurophysiological recordings were limited in time (two times 2-minute EEGs) and statistical power (n=57 abnormal EEGs).
Conclusions: Response rates in patients with normalized EEG taking sertraline were significantly larger than in subjects treated with escitalopram/venlafaxine. This adds to personalized medicine and suggests a possible drug repurposing for sertraline**.**

Gepubliceerd: J Affect Disord 2019 Dec 1;259:67-72
Impact factor: 4.084; Q1

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22. Variable Interpretation of the Dystonia Consensus Classification Items Compromises Its Solidity
van Egmond ME, Contarino MF, Lugtenberg CHA, Peall KJ, Brouwer OF, Fung VSC, Roze E, Stewart RE, Willemsen MA, Wolf NI, de Koning TJ, Tijssen MA

Gepubliceerd: Mov Disord 2019 Feb 6;34(3):317-20
Impact factor: 8.222; Q1

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23. Detecting abnormal electroencephalograms using deep convolutional networks
van Leeuwen KG, Sun H, Tabaeizadeh M, Struck AF, van Putten MJAM, Westover MB

Objectives: : Electroencephalography (EEG) is a central part of the medical evaluation for patients with neurological disorders. Training an algorithm to label the EEG normal vs abnormal seems challenging, because of EEG heterogeneity and dependence of contextual factors, including age and sleep stage. Our objectives were to validate prior work on an independent data set suggesting that deep learning methods can discriminate between normal vs abnormal EEGs, to understand whether age and sleep stage information can improve discrimination, and to understand what factors lead to errors.
Methods: We train a deep convolutional neural network on a heterogeneous set of 8522 routine EEGs from the Massachusetts General Hospital. We explore several strategies for optimizing model performance, including accounting for age and sleep stage.
Results: The area under the receiver operating characteristic curve (AUC) on an independent test set (n=851) is 0.917 marginally improved by including age (AUC=0.924), and both age and sleep stages (AUC=0.925), though not statistically significant.
Conclusions: The model architecture generalizes well to an independent dataset. Adding age and sleep stage to the model does not significantly improve performance. SIGNIFICANCE: Insights learned from misclassified examples, and minimal improvement by adding sleep stage and age suggest fruitful directions for further research**.**

Gepubliceerd: Clin Neurophysiol 2019 Jan;130(1):77-84
Impact factor: 3.675; Q2

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24. Postmortem histopathology of electroencephalography and evoked potentials in postanoxic coma
van Putten MJAM, Jansen C, Tjepkema-Cloostermans MC, Beernink TMJ, Koot R, Bosch F, Beishuizen A, Hofmeijer J

Early EEG patterns and SSEP responses are associated with neurological recovery of comatose patients with postanoxic encephalopathy after cardiac arrest. However, the nature and distribution of brain damage underlying the characteristic EEG and SSEP patterns are unknown. We relate EEG and SSEP findings with results from histological analyses of the brains of eleven non-survivors. With restoration towards continuous rhythms within 24h after cardiac arrest, no signs of structural neuronal damage were observed. Absent SSEP responses were always accompanied by thalamic damage. Pathological burst suppression patterns were associated with a variable degree of neuronal damage to cortex, cerebellum and hippocampus. In patients with additional thalamic involvement, burst-suppression with identical bursts was observed, a characteristic EEG pattern presumably reflecting residual activity from a relatively isolated and severely compromised cortex**.**

Gepubliceerd: Resuscitation 2019 Jan;134:26-32

Impact factor: 4.572; Q1

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25. Hippocampal transcriptome profiling combined with protein-protein interaction analysis elucidates Alzheimer's disease pathways and genes
van Rooij JGJ, Meeter LHH, Melhem S, Nijholt DAT, Wong TH, Rozemuller A, Uitterlinden AG, van Meurs JG, van Swieten JC

Knowledge about the molecular mechanisms driving Alzheimer's disease (AD) is still limited. To learn more about AD biology, we performed whole transcriptome sequencing on the hippocampus of 20 AD cases and 10 age- and sex-matched cognitively healthy controls. We observed 2716 differentially expressed genes, of which 48% replicated in a second data set of 84 AD cases and 33 controls. We used an integrative network-based approach for combining transcriptomic and protein-protein interaction data to find differentially expressed gene modules that may reflect key processes in AD biology. A total of 735 differentially expressed genes were clustered into 33 modules, of which 82% replicated in a second data set, highlighting the robustness of this approach. These 27 modules were enriched for signal transduction, transport, response to stimulus, and several organic and cellular metabolic pathways. Ten modules interacted with previously described AD genes. Our study indicates that analyzing RNA-expression data based on annotated gene modules is more robust than on individual genes. We provide a comprehensive overview of the biological processes involved in AD, and the detected differentially expressed gene modules may provide a molecular basis for future research into mechanisms underlying AD**.**

Gepubliceerd: Neurobiol Aging 2019 Feb;74:225-33
Impact factor: 4.398; Q1

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26. EIF2AK3 variants in Dutch patients with Alzheimer's disease
Wong TH, van der Lee SJ, van Rooij JGJ, Meeter LHH, Frick P, Melhem S, Seelaar H, Ikram MA, Rozemuller AJ, Holstege H, Hulsman M, Uitterlinden A, Neumann M, Hoozemans JJM, van Duijn CM, Rademakers R, van Swieten JC

Next-generation sequencing has contributed to our understanding of the genetics of Alzheimer's disease (AD) and has explained a substantial part of the missing heritability of familial AD. We sequenced 19 exomes from 8 Dutch families with a high AD burden and identified EIF2AK3, encoding for protein kinase RNA-like endoplasmic reticulum kinase (PERK), as a candidate gene. Gene-based burden analysis in a Dutch AD exome cohort containing 547 cases and 1070 controls showed a significant association of EIF2AK3 with AD (OR 1.84 [95% CI 1.07-3.17], p-value 0.03), mainly driven by the variant p.R240H. Genotyping of this variant in an additional cohort from the Rotterdam Study showed a trend toward association with AD (p-value 0.1). Immunohistochemical staining with pPERK and peIF2alpha of 3 EIF2AK3 AD carriers showed an increase in hippocampal neuronal cells expressing these proteins compared with nondemented controls, but no difference was observed in AD noncarriers. This study suggests that rare variants in EIF2AK3 may be associated with disease risk in AD**.**

Gepubliceerd: Neurobiol Aging 2019 Jan;73:229
Impact factor: 4.398; Q1

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27. Predicting outcome in patients with moderate to severe traumatic brain injury using electroencephalography
Haveman ME, van Putten MJAM, Hom HW, Eertman-Meyer CJ, Beishuizen A, Tjepkema-Cloostermans MC

Background: Better outcome prediction could assist in reliable quantification and classification of traumatic brain injury (TBI) severity to support clinical decision-making. We developed a multifactorial model combining quantitative electroencephalography (qEEG) measurements and clinically relevant parameters as proof of concept for outcome prediction of patients with moderate to severe TBI.
Methods: Continuous EEG measurements were performed during the first 7 days of ICU admission. Patient outcome at 12 months was dichotomized based on the Extended Glasgow Outcome Score (GOSE) as poor (GOSE 1-2) or good (GOSE 3-8). Twenty-three qEEG features were extracted. Prediction models were created using a Random Forest classifier based on qEEG features, age, and mean arterial blood pressure (MAP) at 24, 48, 72, and 96 h after TBI and combinations of two time intervals. After optimization of the models, we added parameters from the International Mission for Prognosis And Clinical Trial Design (IMPACT) predictor, existing of clinical, CT, and laboratory parameters at admission. Furthermore, we compared our best models to the online IMPACT predictor.
Results: Fifty-seven patients with moderate to severe TBI were included and divided into a training set (n = 38) and a validation set (n = 19). Our best model included eight qEEG parameters and MAP at 72 and 96 h after TBI, age, and nine other IMPACT parameters. This model had high predictive ability for poor outcome on both the training set using leave-one-out (area under the receiver operating characteristic curve (AUC) = 0.94, specificity 100%, sensitivity 75%) and validation set (AUC = 0.81, specificity 75%, sensitivity 100%). The IMPACT predictor independently predicted both groups with an AUC of 0.74 (specificity 81%, sensitivity 65%) and 0.84 (sensitivity 88%, specificity 73%), respectively.
Conclusions: Our study shows the potential of multifactorial Random Forest models using qEEG parameters to predict outcome in patients with moderate to severe TBI.

Gepubliceerd: Crit Care 2019 Dec 11;23(1):401
Impact factor: 6.959; Q1

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28. Vibrating socks to improve gait in Parkinson's disease.
Koopman CM, Lutters E, Nonnekes J, Bloem BR, van Vugt JPP, Tjepkema-Cloostermans MC.

Gepubliceerd: Parkinsonism Relat Disord. 2019 Dec;69:59-60.
Impact factor: 4.360; Q1

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29. A novel mitochondrial m.4414T>C MT-TM gene variant causing progressive external ophthalmoplegia and myopathy.

Hellebrekers DMEI, Blakely EL, Hendrickx ATM, Hardy SA, Hopton S, Falkous G, de Coo IFM, Smeets HJM, van der Beek NME, Taylor RW.

We report a novel mitochondrial m.4414T>C variant in the mt-tRNAMet (MT-TM) gene in an adult patient with chronic progressive external ophthalmoplegia and myopathy whose muscle biopsy revealed focal cytochrome c oxidase (COX)-deficient and ragged red fibres. The m.4414T>C variant occurs at a strongly evolutionary conserved sequence position, disturbing a canonical base pair and disrupting the secondary and tertiary structure of the mt-tRNAMet. Definitive evidence of pathogenicity is provided by clear segregation of m.4414T>C mutant levels with COX deficiency in single muscle fibres. Interestingly, the variant is present in skeletal muscle at relatively low levels (30%) and undetectable in accessible, non-muscle tissues from the patient and her asymptomatic brother, emphasizing the continuing requirement for a diagnostic muscle biopsy as the preferred tissue for mtDNA genetic investigations of mt-tRNA variants leading to mitochondrial myopathy.

Gepubliceerd: Neuromuscul Disord. 2019 Sep;29(9):693-697
Impact factor: 2.216; Q3

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30. Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease.
Verschuur CVM, Suwijn SR, Boel JA, Post B, Bloem BR, van Hilten JJ, van Laar T, Tissingh G, Munts AG, Deuschl G, Lang AE, Dijkgraaf MGW, de Haan RJ, de Bie RMA; LEAP Study Group, includes Dorresteijn LDA

Background: Levodopa is the main treatment for symptoms of Parkinson's disease. Determining whether levodopa also has a disease-modifying effect could provide guidance as to when in the course of the disease the treatment with this drug should be initiated.
Methods: In a multicenter, double-blind, placebo-controlled, delayed-start trial, we randomly assigned patients with early Parkinson's disease to receive levodopa (100 mg three times per day) in combination with carbidopa (25 mg three times per day) for 80 weeks (early-start group) or placebo for 40 weeks followed by levodopa in combination with carbidopa for 40 weeks (delayed-start group). The primary outcome was the between-group difference in the mean change from baseline to week 80 in the total score on the Unified Parkinson's Disease Rating Scale (UPDRS; scores range from 0 to 176, with higher scores signifying more severe disease). Secondary analyses included the progression of symptoms, as measured by the UPDRS score, between weeks 4 and 40 and the noninferiority of early initiation of treatment to delayed initiation between weeks 44 and 80, with a noninferiority margin of 0.055 points per week.
Results: A total of 445 patients were randomly assigned: 222 to the early-start group and 223 to the delayed-start group. The mean (±SD) UPDRS score at baseline was 28.1±11.4 points in the early-start group and 29.3±12.1 points in the delayed-start group. The change in UPDRS score from baseline to week 80 was -1.0±13.1 points and -2.0±13.0 points, respectively (difference, 1.0 point; 95% confidence interval [CI], -1.5 to 3.5; P=0.44); this finding of no significant between-group difference at week 80 implies that levodopa had no disease-modifying effect. Between weeks 4 and 40, the rate of progression of symptoms, as measured in UPDRS points per week, was 0.04±0.23 in the early-start group and 0.06±0.34 in the delayed-start group

(difference, -0.02; 95% CI, -0.07 to 0.03). The corresponding rates between weeks 44 and 80 were 0.10±0.25 and 0.03±0.28 (difference, 0.07; two-sided 90% CI, 0.03 to 0.10); the difference in the rate of progression between weeks 44 and 80 did not meet the criterion for noninferiority of early receipt of levodopa to delayed receipt. The rates of dyskinesia and levodopa-related fluctuations in motor response did not differ significantly between the two groups.
Conclusions: Among patients with early Parkinson's disease who were evaluated over the course of 80 weeks, treatment with levodopa in combination with carbidopa had no disease-modifying effect. (Funded by the Netherlands Organization for Health Research and Development and others; LEAP Current Controlled Trials number, ISRCTN30518857.).

Gepubliceerd: N Engl J Med. 2019 Jan 24;380(4):315-324.
Impact factor: 70.670; Q1

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31. Traumatic brain injuries in older adults - causes and consequences
Hageman G, de Koning ME, Roks G, Nihom J, van der Naalt J

Falls occur frequently among older adults. In the Netherlands almost 100,000 adults aged over 65 years visit the emergency department each year. In approximately half of all fall-related injuries among elderly, hospital admission is necessary. In 15% of fall-related injuries among elderly traumatic brain injury is involved. This article describes a study among 211 elderly with a mild traumatic brain injury after a fall. Trauma mechanisms and the role of underlying causes like medication use and comorbidities are described. Preventive strategies will also be addressed.

Gepubliceerd: Tijdschr Neurol Neurochir 2019;120(6):207-11
Impact factor: nvt

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32. Biomarkers in mild traumatic brain injury
Hageman G, Nihom J, de Koning ME, van der Naalt J

Clinical neurological investigation and brain CT scanning in the Emergency Department are most important in the assessment of patients with mild traumatic brain injury (mTBI). In the Netherlands biomarkers are not used routinely. However, several biomarkers have been investigated in predicting intracranial complications after mTBI. Specifically, the glial protein S-100 beta is part of the Scandinavian guidelines of traumatic brain injury. In this paper we review the results of S-100 beta, glial fibrillary acidic protein (GFAP), ubiquitin c- terminal hydrolase (UCH-L1), tau and neurofilament light in the assessment of patients with mTBI. Low values of S-100 beta, GFAP and UCH-L1 accurately predict a normal brain CT-scan in mTBI. Clinical application could lead to a reduction of the number of CT-scans. We therefore recommend these biomarkers to become part of the upcoming revision of the Dutch guideline for mild traumatic brain injury. High values of GFAP and UCH-L1 may predict intracranial complications, although there is still insufficient evidence.

Gepubliceerd: Tijdschr Neurol Neurochir 2019;120(3):111-7
Impact factor: nvt

33. LRP10 variants in Parkinson's disease and dementia with Lewy bodies in the South-West of the Netherlands.
Vergouw LJM, Ruitenberg A, Wong TH, Melhem S, Breedveld GJ, Criscuolo C, De Michele G, de Jong FJ, Bonifati V, van Swieten JC, Quadri M

Objective: To analyse LRP10 variants, recently associated with the development of Parkinson's disease (PD), Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), in a series of patients and controls from the South-West of the Netherlands (Walcheren).
Methods: A series of 130 patients with PD, PDD or DLB were clinically examined, and a structured questionnaire used to collect information about family history of PD and dementia. The entire LRP10 coding region was sequenced by Sanger methods in all patients, and haplotype analysis was performed for one recurrent LRP10 variant. The fragments containing possibly pathogenic LRP10 variants were sequenced in 62 unaffected control subjects from the same region. Other known PD-associated genes were analyzed by exome sequencing and gene dosage in the carriers of LRP10 variants.
Results: Four patients were carriers of a rare heterozygous, possibly pathogenic LRP10 variant: p.Arg151Cys, p.Arg263His, and p.Tyr307Asn. None of these variants was detected among the controls, nor were additional mutations identified in known PD-associated genes in the four LRP10 variant carriers. The previously reported p.Tyr307Asn variant was identified in two patients (with PD and PDD), who are connected genealogically within six generations, and in one of their relatives with cognitive decline. Haplotype analysis suggests a common founder for the p.Tyr307Asn variant carriers analyzed.
Discussion: We report three possibly pathogenic LRP10 variants in patients with PD and PDD from a local Dutch population. The identification of additional patients carrying the p.Tyr307Asn variant provides some

Gepubliceerd: Parkinsonism Relat Disord. 2019 Aug;65:243-7
Impact factor: 4.360; Q1

Totale impact factor: 196.959
Gemiddelde impact factor: 5.968

Aantal artikelen 1e, 2e of laatste auteur: 20
Totale impact factor: 73.617
Gemiddelde impact factor: 3.681

Orthopedie

1. Direct Anterior Approach for One-Stage Bilateral Total Hip Arthroplasty in an ASA 3 Wheelchair-Dependent Woman
Barvelink BB, Hooghof JTA, Brokelman RBGR

This case report involves a 79-year-old wheelchair-dependent woman with bilateral destructive coxarthrosis, requiring total hip arthroplasty (THA). Mobilization and transfers were unbearable due to the bilateral involvement of her hips. Performing unilateral THA would not be sufficient due to the coexisting pain from the contralateral side. Therefore, the decision was made to perform bilateral THA in one stage using the direct anterior approach (DAA). One-stage bilateral THA (1-SBTHA) using the DAA in ASA 3 patients is not previously described in the literature. The procedure was completed as planned, without any major perioperative complications. Eight weeks postoperatively, the patient was able to mobilize unaccompanied using a walker. She regained her mobility and independence. This outcome suggests that 1-SBTHA using DAA can be considered for disabling coxarthrosis in carefully selected ASA 3 patients. DAA is the superior approach for 1-SBTHA, due to decreased muscle damage leading to early mobilization with improved gait. Another benefit of DAA is that both hips can be draped simultaneously without repositioning the patient during the procedure.

Gepubliceerd: Case Rep Orthop 2019;2019:5183578
Impact factor: 0; nvt

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2. A comparative health care inventory for primary hip arthroplasty between Germany versus the Netherlands. Is there a downside effect to fast-track surgery with regard to patient satisfaction and functional outcome?
Fussenich W, Gerhardt DM, Pauly T, Lorenz F, Olieslagers M, Braun C, van Susante JL

Background: Treatment and rehabilitation protocol for hip arthroplasty differs between Germany and the Netherlands. The Dutch system promotes fast-track surgery whereas in Germany conventional care is provided with a longer hospital stay including rehabilitation. Clinical outcome, patient satisfaction and costs in both treatment protocols were compared in a prospective setup.
Material and methods: This prospective cohort study included patients allocated for primary THA in 3 German and 1 Dutch hospital in the border region. Patient-reported outcome scores (PROMS) were measured pre- and postoperatively at 6 and 12 months including the Oxford Hip Score, SF12 survey, visual analogue scale for satisfaction and pain. Length of hospitalisation and availability of postoperative rehabilitation were recorded. In addition, a total cost estimation was calculated using health insurers data.
Results: A total of 360 consecutive patients were included; 175 THA in Germany compared to 185 THA in the Netherlands. No cross-border healthcare was encountered in both cohorts. Mean length of hospitalisation was 11.3 (range 6-23) days in Germany, compared to 4.4 (range 3-25) days in the Netherlands. In Germany 92% of the patients was discharged with inpatient (72%) or outpatient (20%)

rehabilitation, compared to 21% with only inpatient rehabilitation in the Netherlands. No significant differences were measured regarding the PROMS and patient satisfaction between both countries. Due to profound differences in health care financing only a global cost estimation could be made and no major differences were encountered.
Conclusion: Germany and the Netherlands both offer highly protocolled care for THA with comparable functional outcome and patient satisfaction with treatment after 12 months. Despite the length of hospitalisation in Germany is significantly longer including a more intensive rehabilitation programme, no significant differences were recorded regarding functional outcome nor patient satisfaction compared to fast-track surgery performed in the Netherlands.

Gepubliceerd: Hip Int 2019 Sep 11;1120700019876881
Impact factor: 1.250; Q3

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3. Bone sarcoma incidence in the Netherlands
Goedhart LM, Ho VKY, Dijkstra PDS, Schreuder HWB, Schaap GR, Ploegmakers JJW, van der Geest ICM, van de Sande MAJ, Bramer JA, Suurmeijer AJH, Jutte PC

Aims: Chondrosarcoma, osteosarcoma and Ewing sarcoma form the majority of malignant primary tumours of bone. High-grade bone sarcomas require intensive treatment due to their rapid and invasive growth pattern and metastasising capabilities. This nationwide study covers overall incidence, treatment and survival patterns of bone sarcomas in a 15-year period (2000-2014) in the total population of the Netherlands.
Patients and methods: Data for this study were derived from the Netherlands Cancer Registry, which receives primary notification from the national pathology database. Classification and categorisation was based on the ICD-O-3 classification and the WHO classification 2013 applied according to our clinicopathological expertise. Overall incidence over the 15-year-period was calculated as a rate per 100,000 person-years (using the European Standardised Rate, ESR). Survival was analysed with Kaplan-Meier curves and Cox proportional hazards regression.
Results: Incidence for high-grade chondrosarcoma (n = 429) was estimated at 0.15 per 100,000 ESR, and 5-year overall survival at 65.9% (95% confidence interval (CI): 61.0%-70.4%). Incidence for high-grade central osteosarcoma (n = 605) was estimated at 0.25 per 100,000 ESR and 5-year survival at 53.9% (95%CI: 49.7%-58.0%). Ewing sarcoma incidence (n = 334) was estimated at 0.15 per 100,000 ESR and 5-year survival at 59.3% (95%CI: 53.5%-64.6%). For high-grade central osteosarcoma, treatment at a bone tumour centre was associated with better survival (HR 0.593).
Conclusions: This study provides comprehensive incidence estimates for all the main primary bone sarcomas over a 15-year time period in a Northern European country with little migration. Centralisation of bone sarcoma care improves the clinical outcome in osteosarcoma.

Gepubliceerd: Cancer Epidemiol 2019 Jun;60:31-8
Impact factor: 2.619; Q2

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4. Reasons for continuing physiotherapy treatment after a high-intensity physyiotherapy program in patients after total knee arthroplasty: a mixed-methods study
Harmelink K, Nijhuis-van der Sanden R, Zeegers E, Hullegie W, Van der Wees P, Staal B

Background: Patients after total knee arthroplasty treated with a 10-day high-intensity physiotherapy program in a resort were expected to recover fast without need for a longer physiotherapy treatment period.Objective: To explore the expectations and experiences of patients with total knee arthroplasty following the high-intensity physiotherapy program, including the perceived recovery level at discharge, and reasons for (not) adhering to the given advice at discharge (being either continuing with or refraining from further physiotherapy treatment).Design: A mixed-methods approach: semi-structured interviews were held and were then used to develop items and answer categories for a survey.Methods: Fifteen patients participated in semi-structured interviews, which focused on expectations and experiences related to the total knee arthroplasty and physiotherapy program, the perceived recovery level at the moment of discharge, and the reasons for the advice at discharge (continuing with or refraining from physiotherapy treatment) being followed. A deductive thematic analysis of those interviews was used to develop a survey, which was sent to the total cohort of 60 patients. Logistic regression models were estimated to determine which factors were associated with the continuation of physiotherapy treatment and (not) following the advice.
Results: Four themes were identified: (1) confidence of independent recovery; (2) experiencing residual complaints; (3) expecting further improvement of physical fitness; and (4) preferring to be supervised by a healthcare professional. These themes were covered by 14 items in the survey. In total, 55 out of 60 patients completed the survey. Out of 36 patients, 23 continued with physiotherapy treatment despite an adequate level of recovery. Five out of 19 patients, who were advised to continue with physiotherapy treatment, decided to refrain. Advice to continue with physiotherapy treatment was followed more often than advice to refrain from physiotherapy treatment (OR 0.09; 95%CI 0.01-0.85). Reasons for continuing with physiotherapy treatment were residual complaints, the expectation that their physical fitness could be improved and preferring to be supervised by a healthcare professional. In contrast, patients who refrained from physiotherapy, despite being advised to continue, were self-confident that they could do exercises by themselves.
Conclusions: A substantial proportion of patients continued with physiotherapy treatment because they expected that a higher level of recovery could be reached. The level of self-confidence to recover on their own seemed to be an important factor in deciding to continue with or refrain from physiotherapy treatment. It would be helpful to focus on self-management skills during the high-intensity physiotherapy program following total knee arthroplasty.

Gepubliceerd: Physiother Theory Pract 2019 Nov 24;1-16
Impact factor: 1.158; Q4

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5. High incidence of early periprosthetic joint infection following total hip arthroplasty with concomitant or previous hardware removal
Scholten R, Fussenich W, Somford MP, van Susante JLC

Introduction: Hardware removal preceding total hip arthroplasty may increase the risk of prosthetic joint infection (PJI). Whether hardware removal and total hip arthroplasty (THA) should be performed in a single- or two-stage procedure remains controversial. In this comparative retrospective study, the incidence of PJI following either single- or two-stage THA with hardware removal was assessed in a consecutive series.
Patients and methods: All patients that underwent THA preceded by hardware removal from January 2006 until March 2018 were retrospectively reviewed and checked for the occurrence of early PJI. Recognized risk factors for PJI at the time of surgery were evaluated and the incidence of early PJI was compared between one- and two-stage THA regarding hardware removal.
Results: 145 patients underwent THA and hardware removal (52 two-stage surgery and 93 single-stage surgery). There were no significant differences between both groups regarding pre-operative hemoglobulin levels, time interval between internal fixation and THA, antibiotic-loaded-cement use, BMI and ASA classification. Overall the incidence of early PJI was 6.9%. The incidence of PJI was 8.6% in the single-stage group versus 3.8% in the two-stage group (P = 0.234).
Conclusion: Irrespective of single- or two-stage procedures, a high incidence of PJI was encountered. Despite non-significance, a trend towards a higher proportion of patients developing PJI after single-stage surgery was encountered. We recommend a two-stage surgical procedure regarding hardware removal and THA in patients that are expected to tolerate this surgical strategy. When considering a one-stage procedure, it should be preceded by a thorough pre-operative workup including joint aspiration and serum determination of inflammatory parameters. Multiple tissue samples should be obtained during hardware removal in either one- or two-stage procedures since the risk for development of PJI is relevant.

Gepubliceerd: Arch Orthop Trauma Surg 2019 Aug;139(8):1051-6
Impact factor: 1.973; Q2

Totale impact factor: 7.000
Gemiddelde impact factor: 1.400

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 5.842
Gemiddelde impact factor: 1.461

Pathologie

1. Computer aided quantification of intratumoral stroma yields an independent prognosticator in rectal cancer
Geessink OGF, Baidoshvili A, Klaase JM, Ehteshami Bejnordi B, Litjens GJS, van Pelt GW, Mesker WE, Nagtegaal ID, Ciompi F, van der Laak JAWM

Purpose: Tumor-stroma ratio (TSR) serves as an independent prognostic factor in colorectal cancer and other solid malignancies. The recent introduction of digital pathology in routine tissue diagnostics holds opportunities for automated TSR analysis. We investigated the potential of computer-aided quantification of intratumoral stroma in rectal cancer whole-slide images.
Methods: Histological slides from 129 rectal adenocarcinoma patients were analyzed by two experts who selected a suitable stroma hot-spot and visually assessed TSR. A semi-automatic method based on deep learning was trained to segment all relevant tissue types in rectal cancer histology and subsequently applied to the hot-spots provided by the experts. Patients were assigned to a 'stroma-high' or 'stroma-low' group by both TSR methods (visual and automated). This allowed for prognostic comparison between the two methods in terms of disease-specific and disease-free survival times.
Results: With stroma-low as baseline, automated TSR was found to be prognostic independent of age, gender, pT-stage, lymph node status, tumor grade, and whether adjuvant therapy was given, both for disease-specific survival (hazard ratio = 2.48 (95% confidence interval 1.29-4.78)) and for disease-free survival (hazard ratio = 2.05 (95% confidence interval 1.11-3.78)). Visually assessed TSR did not serve as an independent prognostic factor in multivariate analysis.
Conclusions: This work shows that TSR is an independent prognosticator in rectal cancer when assessed automatically in user-provided stroma hot-spots. The deep learning-based technology presented here may be a significant aid to pathologists in routine diagnostics.

Gepubliceerd: Cell Oncol (Dordr) 2019 Jun;42(3):331-41
Impact factor: 5.020; Q1

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2. Prediction and clinical utility of a contralateral breast cancer risk model
Giardiello D, Steyerberg EW, Hauptmann M, Adank MA, Akdeniz D, Blomqvist C, Bojesen SE, Bolla MK, Brinkhuis M, Chang-Claude J, Czene K, Devilee P, Dunning AM, Easton DF, Eccles DM, Fasching PA, Figueroa J, Flyger H, Garcia-Closas M, Haeberle L, Haiman CA, Hall P, Hamann U, Hopper JL, Jager A, Jakubowska A, Jung A, Keeman R, Kramer I, Lambrechts D, Le Marchand L, Lindblom A, Lubinski J, Manoochehri M, Mariani L, Nevanlinna H, Oldenburg HSA, Pelders S, Pharoah PDP, Shah M, Siesling S, Smit VTHB, Southey MC, Tapper WJ, Tollenaar RAEM, van den Broek AJ, van Deurzen CHM, van Leeuwen FE, van Ongeval C, Van't Veer LJ, Wang Q, Wendt C, Westenend PJ, Hooning MJ, Schmidt MK

Background: Breast cancer survivors are at risk for contralateral breast cancer (CBC), with the consequent burden of further treatment and potentially less favorable

prognosis. We aimed to develop and validate a CBC risk prediction model and evaluate its applicability for clinical decision-making.
Methods: We included data of 132,756 invasive non-metastatic breast cancer patients from 20 studies with 4682 CBC events and a median follow-up of 8.8 years. We developed a multivariable Fine and Gray prediction model (PredictCBC-1A) including patient, primary tumor, and treatment characteristics and BRCA1/2 germline mutation status, accounting for the competing risks of death and distant metastasis. We also developed a model without BRCA1/2 mutation status (PredictCBC-1B) since this information was available for only 6% of patients and is routinely unavailable in the general breast cancer population. Prediction performance was evaluated using calibration and discrimination, calculated by a time-dependent area under the curve (AUC) at 5 and 10 years after diagnosis of primary breast cancer, and an internal-external cross-validation procedure. Decision curve analysis was performed to evaluate the net benefit of the model to quantify clinical utility.
Results: In the multivariable model, BRCA1/2 germline mutation status, family history, and systemic adjuvant treatment showed the strongest associations with CBC risk. The AUC of PredictCBC-1A was 0.63 (95% prediction interval (PI) at 5 years, 0.52-0.74; at 10 years, 0.53-0.72). Calibration-in-the-large was -0.13 (95% PI: -1.62-1.37), and the calibration slope was 0.90 (95% PI: 0.73-1.08). The AUC of Predict-1B at 10 years was 0.59 (95% PI: 0.52-0.66); calibration was slightly lower. Decision curve analysis for preventive contralateral mastectomy showed potential clinical utility of PredictCBC-1A between thresholds of 4-10% 10-year CBC risk for BRCA1/2 mutation carriers and non-carriers.
Conclusions: We developed a reasonably calibrated model to predict the risk of CBC in women of European-descent; however, prediction accuracy was moderate. Our model shows potential for improved risk counseling, but decision-making regarding contralateral preventive mastectomy, especially in the general breast cancer population where limited information of the mutation status in BRCA1/2 is available, remains challenging.

Gepubliceerd: Breast Cancer Res 2019 Dec 17;21(1):144
Impact factor: 5.676; Q1

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3. A 37-Year-Old Woman With Recurrent Hemoptysis
Schoonbeek RC, Wagenaar M, Baidoshvili A, van Veen IHPA

Case presentation: A 37-year-old woman presented with a 2-month history of recurrent hemoptysis and coughing. Her symptoms started 2 months after the delivery of her third child. In total, she endured four episodes of hemoptysis. All pregnancies were induced by intracytoplasmic sperm injections. She lacked a pulmonary or smoking history and had no history of foreign body aspiration or intubation. There was no dyspnea, dysphagia, fever, or chest pain, and the patient did not complain of purulent sputum. She currently did not use medication and was generally in good health.

Gepubliceerd: Chest 2019 Oct;156(4):e81-e84
Impact factor: 9.657; Q1

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4. Validation of Whole-slide Digitally Imaged Melanocytic Lesions: Does Z-Stack Scanning Improve Diagnostic Accuracy?
Sturm B, Creytens D, Cook MG, Smits J, van Dijk MCRF, Eijken E, Kurpershoek E, Kusters-Vandevelde HVN, Ooms AHAG, Wauters C, Blokx WAM, van der Laak JAWM

Background: Accurate diagnosis of melanocytic lesions is challenging, even for expert pathologists. Nowadays, whole-slide imaging (WSI) is used for routine clinical pathology diagnosis in several laboratories. One of the limitations of WSI, as it is most often used, is the lack of a multiplanar focusing option. In this study, we aim to establish the diagnostic accuracy of WSI for melanocytic lesions and investigate the potential accuracy increase of z-stack scanning. Z-stack enables pathologists to use a software focus adjustment, comparable to the fine-focus knob of a conventional light microscope.
Materials and Methods: Melanocytic lesions (n = 102) were selected from our pathology archives: 35 nevi, 5 spitzoid tumors of unknown malignant potential, and 62 malignant melanomas, including 10 nevoid melanomas. All slides were scanned at a magnification comparable to use of a x40 objective, in z-stack mode. A ground truth diagnosis was established on the glass slides by four academic dermatopathologists with a special interest in the diagnosis of melanoma. Six nonacademic surgical pathologists subspecialized in dermatopathology examined the cases by WSI.
Results: An expert consensus diagnosis was achieved in 99 (97%) of cases. Concordance rates between surgical pathologists and the ground truth varied between 75% and 90%, excluding nevoid melanoma cases. Concordance rates of nevoid melanoma varied between 10% and 80%. Pathologists used the software focusing option in 7%-28% of cases, which in 1 case of nevoid melanoma resulted in correcting a misdiagnosis after finding a dermal mitosis.
Conclusion: Diagnostic accuracy of melanocytic lesions based on glass slides and WSI is comparable with previous publications. A large variability in diagnostic accuracy of nevoid melanoma does exist. Our results show that z-stack scanning, in general, does not increase the diagnostic accuracy of melanocytic.

Gepubliceerd: J Pathol Inform 2019;10:6
Impact factor: 2.880; Q2

Totale impact factor: 23.233
Gemiddelde impact factor: 5.808

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 5.020
Gemiddelde impact factor: 5.020

Plastische chirurgie

1. Factors Associated With Patients' Perceived Importance of Opioid Prescribing Policies in an Orthopedic Hand Surgery Practice
Bargon CA, Zale EL, Magidson J, Chen N, Ring D, Vranceanu AM

Purpose: The purpose of this study was to survey the attitudes and beliefs about opioids and opioid prescribing policies among patients presenting to an orthopedic hand surgery practice.
Methods: Patients (n = 118; median age, 49 years) who presented to their regularly scheduled appointment at a major urban university medical center completed surveys assessing their sociodemographic and clinical characteristics, beliefs about prescription opioids, beliefs about opioid prescribing policies, and perceived importance of opioid prescribing policies in the department.
Results: Many patients were aware of potential risks of opioids (eg, 80% are aware of addictive properties) and would support opioid prescribing policies that aim to decrease opioid misuse and diversion. However, a small but important number of patients have concerning beliefs about prescription opioids (eg, 28% believe opioids work well for long-term pain) or believe that doctors should prescribe "as much medication as the patient needs" (7%). The vast majority (98%) indicated that they would like more education on opioids and that information about prescription opioids should be provided to all patients in orthopedic practices. Patients with higher educational attainment reported a greater perceived importance of opioid prescribing policies.
Conclusions: The results of this study suggest that opioid prescribing strategies that promote safe and effective alleviation of pain and optimal opioid stewardship will be well received by patients.
Clinical relevance: Efforts to develop and test the effects of opioid prescribing policies and nonopioid pain relief strategies on opioid prescribing are merited.

Gepubliceerd: J Hand Surg Am 2019;44(4):340.e1-340.e8
Impact factor: 2.090; Q2

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2. The Dutch Breast Implant Registry: Registration of Breast Implant-Associated Anaplastic Large Cell Lymphoma-A Proof of Concept
Becherer BE, de Boer M, Spronk PER, Bruggink AH, de Boer JP, van Leeuwen FE, Mureau MAM, van der Hulst RRJW, de Jong D, Rakhorst HA

Background: The Dutch Breast Implant Registry (DBIR) was established in April of 2015 and currently contains information on 38,000 implants in 18,000 women. As a clinical registry, it evaluates the quality of breast implant surgery, including adverse events such as breast implant-associated (BIA) anaplastic large cell lymphoma (ALCL). To examine the efficacy of the DBIR, the capture rate of BIA-ALCL was compared to the registration of BIA-ALCL in the Dutch Nationwide Network and Registry of Histo- and Cytopathology (PALGA) as a gold standard, in combination with matching these databases to obtain complementary information.
Methods: All BIA-ALCL patients diagnosed and registered in The Netherlands in 2016 and 2017 were identified separately in the PALGA and DBIR databases. In

addition, both databases were matched using indirect key identifiers. Pathologic information from the PALGA and clinical and device characteristics from the DBIR were obtained for all patients.
Results: Matching of both databases gave a capture rate of BIA-ALCL in the DBIR of 100 percent (n = 6) in 2016 and 70 percent (n = 7) in 2017. In total, 17 patients were identified in the PALGA, of which 14 patients were also identified in the DBIR; three patients were not registered; and 10 patients were registered false-positive. Of all confirmed patients, symptoms, staging results, treatment, and implant information were registered.
Conclusions: Currently, the DBIR contains 2 full registration years and captures most of the BIA-ALCL patients despite overestimation. Therefore, pathology confirmation remains essential. By matching these databases, complementary clinical and implant information could be retrieved, establishing the DBIR as an essential postmarketing surveillance system for health risk assessments.

Gepubliceerd: Plast Reconstr Surg 2019 May;143(5):1298-306
Impact factor: 3.946; Q1

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3. Defining Quality Indicators for Breast Device Surgery: Using Registries for Global Benchmarking
Begum H, Vishwanath S, Merenda M, Tacey M, Dean N, Elder E, Mureau M, Bezic R, Carter P, Cooter RD, Deva A, Earnest A, Higgs M, Klein H, Magnusson M, Moore C, Rakhorst H, Saunders C, Stark B, Hopper I

Breast device registries monitor devices encompassing breast implants, tissue expanders and dermal matrices, and the quality of care and patient outcomes for breast device surgery. Defining a standard set of quality indicators and risk adjustment factors will enable consistency and adjustment for case-mix in benchmarking quality of care across breast implant registries. This study aimed to develop a set of quality indicators to enable assessment and reporting of quality of care for breast device surgery which can be applied globally.
Methods: A scoping literature review was undertaken, and potential quality indicators were identified. Consensus on the final list of quality indicators was obtained using a modified Delphi approach. This process involved a series of online surveys, and teleconferences over 6 months. The Delphi panel included participants from various countries and representation from surgical specialty groups including breast and general surgeons, plastic and reconstructive surgeons, cosmetic surgeons, a breast-care nurse, a consumer, a devices regulator (Therapeutic Goods Administration), and a biostatistician. A total of 12 candidate indicators were proposed: Intraoperative antibiotic wash, intraoperative antiseptic wash, preoperative antibiotics, nipple shields, surgical plane, volume of implant, funnels, immediate versus delayed reconstruction, time to revision, reoperation due to complications, patient satisfaction, and volume of activity.
Results: Three of the 12 proposed indicators were endorsed by the panel: preoperative intravenous antibiotics, reoperation due to complication, and patient reported outcome measures.
Conclusion: The 3 endorsed quality indicator measures will enable breast device registries to standardize benchmarking of care internationally for patients undergoing breast device surgery.

Gepubliceerd: Plast Reconstr Surg Glob Open 2019 Aug;7(8):e2348
Impact factor: 0; nvt

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4. International and Geographic Trends in Gender Authorship within Plastic Surgery
Bucknor A, Peymani A, Kamali P, Epstein S, Chen AD, Bletsis P, Chattha A, Mathijssen I, Rakhorst H, Lin SJ

Background: Professional advancement in academic plastic surgery may depend on scholarly activity. The authors evaluate gender-based publishing characteristics in three international plastic surgery journals.
Methods: A retrospective review of all articles published in 2016 in the following journals was undertaken: Plastic and Reconstructive Surgery, Journal of Plastic, Reconstructive and Aesthetic Surgery, European Journal of Plastic Surgery, Annals of Surgery, and New England Journal of Medicine. Data were collected on lead author gender (first or senior author) and differences in author gender proportions, by journal, by article topic, and by geographic location were evaluated.
Results: Overall, 2610 articles were retrieved: 34.1 percent were from plastic surgery journals, 12.8 percent were from the Annals of Surgery, and 53.1 percent were from the New England Journal of Medicine. There was a lower proportion of female lead authors among plastic surgery journals compared with the Annals of Surgery and the New England Journal of Medicine (31 percent versus 39 percent versus 39 percent; $p = 0.001$). There were no differences in female lead author geographic location in the Annals of Surgery or the New England Journal of Medicine; within the plastic surgery journals, there were differences ($p = 0.005$), including a lower proportion arising from East Asia (15 percent) and a higher proportion arising from Canada (48 percent). Within plastic surgery, Plastic and Reconstructive Surgery had the lowest proportion of female lead author ($p < 0.001$). The proportion of female lead author varied by article topic ($p < 0.001$) and was notably higher in breast (45.6 percent) and lower in head and neck/craniofacial-orientated articles (25.0 percent).
Conclusions: There are gender disparities in three mainstream plastic surgery journals-Plastic and Reconstructive Surgery, the Journal of Plastic, Reconstructive and Aesthetic Surgery, the European Journal of Plastic Surgery-and there are lower proportions of lead female authorship compared with the Annals of Surgery and the New England Journal of Medicine. Further research should focus on understanding any geographic disparities that may exist.

Gepubliceerd: Plast Reconstr Surg 2019 Oct;144(4):1010-6
Impact factor: 3.946; Q1

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5. Current Risk Estimate of Breast Implant-Associated Anaplastic Large Cell Lymphoma in Textured Breast Implants
Collett DJ, Rakhorst H, Lennox P, Magnusson M, Cooter R, Deva AK

Background: With breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) now accepted as a unique (iatrogenic) subtype of ALCL directly associated with textured breast implants, we are now at a point where a sound epidemiologic

profile and risk estimate are required. The aim of this article is to provide a comprehensive and up-to-date global review of the available epidemiologic data and literature relating to the incidence, risk, and prevalence of BIA-ALCL.
Methods: All current literature relating to the epidemiology of BIA-ALCL was reviewed. Barriers relating to sound epidemiologic study were identified, and trends relating to geographical distribution, prevalence of breast implants, and implant characteristics were analyzed.
Results: Significant barriers exist to the accurate estimate of both the number of women with implants (denominator) and the number of cases of BIA-ALCL (numerator), including poor registries, underreporting, lack of awareness, cosmetic tourism, and fear of litigation. The incidence and risk of BIA-ALCL have increased dramatically from initial reports of 1 per million to current estimates of 1/2,832, and is largely dependant on the "population" (implant type and characteristics) examined and increased awareness of the disease.
Conclusions: Although many barriers stand in the way of calculating accurate estimates of the incidence and risk of developing BIA-ALCL, steady progress, international registries, and collegiality between research teams are for the first time allowing early estimates. Most striking is the exponential rise in incidence over the last decade, which can largely be explained by the increasingly specific implant subtypes examined-driven by our understanding of the pathologic mechanism of the disease. High-textured high-surface area implants (grade 4 surface) carry the highest risk of BIA-ALCL (1/2,832).

Gepubliceerd: Plast Reconstr Surg 2019 Mar;143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma):30S-40S
Impact factor: 3.946; Q1

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6. Evaluating the collection, comparability and findings of six global surgery indicators
Holmer H, Bekele A, Hagander L, Harrison EM, Kamali P, Ng-Kamstra JS, Khan MA, Knowlton L, Leather AJM, Marks IH, Meara JG, Shrime MG, Smith M, Soreide K, Weiser TG, Davies J

Background: In 2015, six indicators were proposed to evaluate global progress towards access to safe, affordable and timely surgical and anaesthesia care. Although some have been adopted as core global health indicators, none has been evaluated systematically. The aims of this study were to assess the availability, comparability and utility of the indicators, and to present available data and updated estimates.
Methods: Nationally representative data were compiled for all World Health Organization (WHO) member states from 2010 to 2016 through contacts with official bodies and review of the published and grey literature, and available databases. Availability, comparability and utility were assessed for each indicator: access to timely essential surgery, specialist surgical workforce density, surgical volume, perioperative mortality, and protection against impoverishing and catastrophic expenditure. Where feasible, imputation models were developed to generate global estimates.
Results: Of all WHO member states, 19 had data on the proportion of the population within 2h of a surgical facility, 154 had data on workforce density, 72 reported number

of procedures, and nine had perioperative mortality data, but none could report data on catastrophic or impoverishing expenditure. Comparability and utility were variable, and largely dependent on different definitions used. There were sufficient data to estimate that worldwide, in 2015, there were 2 038 947 (i.q.r. 1 884 916-2 281 776) surgeons, obstetricians and anaesthetists, and 266.1 (95 per cent c.i. 220.1 to 344.4) million operations performed.
Conclusion: Surgical and anaesthesia indicators are increasingly being adopted by the global health community, but data availability remains low. Comparability and utility for all indicators require further resolution.

Gepubliceerd: Br J Surg 2019 Jan;106(2):e138-e150
Impact factor: 5.572; Q1

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7. Immediate Breast Reconstruction in The Netherlands and the United States: A Proof-of-Concept to Internationally Compare Quality of Care Using Cancer Registry Data
Kamali P, van Bommel A, Becherer B, Cooter R, Mureau MAM, Pusic A, Siesling S, van der Hulst RRJW, Lin SJ, Rakhorst H

Background: Studies based on large-volume databases have made significant contributions to research on breast cancer surgery. To date, no comparison between large-volume databases has been made internationally. This is the first proof-of-concept study exploring the feasibility of combining two existing operational databases of The Netherlands and the United States, focusing on breast cancer care and immediate breast reconstruction specifically.313/291
Methods: The National Breast Cancer Organization The Netherlands Breast Cancer Audit (NBCA) (2011 to 2015) and the U.S. Surveillance, Epidemiology, and End Results (SEER) database (2010 to 2013) were compared on structure and content. Data variables were grouped into general, treatment-specific, cancer-specific, and follow-up variables and were matched. As proof-of-concept, mastectomy and immediate breast reconstruction rates in patients diagnosed with invasive breast cancer or ductal carcinoma in situ were analyzed.
Results: The NBCA included 115 variables and SEER included 112. The NBCA included significantly more treatment-specific variables (n = 46 versus 6), whereas the SEER database included more cancer-specific variables (n = 74 versus 26). In patients diagnosed with breast cancer or ductal carcinoma in situ, immediate breast reconstruction was performed in 19.3 percent and 24.0 percent of the breast cancer cohort and 44.0 percent and 35.3 percent of the ductal carcinoma in situ cohort in the NBCA and SEER, respectively. Immediate breast reconstruction rates increased significantly over time in both data sets.
Conclusions: This study provides a first overview of available registry data on breast cancer care in The Netherlands and the United States, and revealed limited data on treatment in the United States. Comparison of treatment patterns of immediate breast reconstruction showed interesting differences. The authors advocate the urgency for an international database with alignment of (treatment) variables to improve quality of breast cancer care for patients across the globe.

Gepubliceerd: Plast Reconstr Surg 2019 Oct;144(4):565e-74e
Impact factor: 3.946; Q1

8. Arm sling after carpal tunnel surgery: myth or evidence based?
Kroeze M, Rakhorst H, Houpt P

Arm sling elevation is widely used after hand surgery to prevent swelling and pain. This prospective cohort study investigated whether arm sling elevation has any value after carpal tunnel release surgery. Patients were assigned to one of two groups after carpal tunnel release: with or without arm sling elevation. The primary outcome was postoperative swelling. Secondary outcomes were pain and symptom relief and functional outcome. Volumetric analysis showed no significant difference between the sling and non-sling group. Pain scores and improvement of symptom severity and functional status scores were similar for both groups. Thirty-eight per cent found the sling uncomfortable. These results do not support routine use of arm sling elevation after carpal tunnel release. Level of evidence: III.

Gepubliceerd: J Hand Surg Eur Vol 2019 Oct 16;1753193419880312
Impact factor: 2.225; Q2

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9. Breast Implant Illness: A Way Forward
Magnusson MR, Cooter RD, Rakhorst H, McGuire PA, Adams WP, Jr., Deva AK

The link between breast implants and systemic disease has been reported since the 1960s. Although many studies have looked at either supporting or refuting its existence, the issue still persists and has now been labeled "breast implant illness." The rise of patient advocacy and communication through social media has led to an increasing number of presentations to plastic surgeons. This article summarizes the history of breast implants and systemic disease, critically analyzes the literature (and any associated deficiencies), and suggests a way forward through systematic scientific study.

Gepubliceerd: Plast Reconstr Surg 2019 Mar;143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma):74S-81S
Impact factor: 3.946; Q1

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10. Reoperation After Operative Fixation of Proximal Interphalangeal Joint Fractures
Oflazoglu K, Wilkens SC, Rakhorst H, Ring D, Chen NC

Background: The purpose of this study was to determine the reoperation rate and what factors are associated with reoperation of proximal interphalangeal (PIP) joint fractures.
Methods: We identified 161 surgically treated PIP joint fractures between 2004 and 2015 at 2 academic medical systems. Demographic, injury, radiographic, and treatment data that might be associated with reoperation were collected. Bivariate analysis was performed. Factors identified during bivariate analysis with a $P < .10$ were entered into a multivariable logistic regression analysis.

Results: Of the 161 fingers, 25 underwent revision surgery. Open fracture was independently associated with revision surgery. The most common indication for reoperation was joint stiffness (35%). In a subanalysis of 111 closed fractures, no factors were associated with revision surgery. **Conclusions:** Soft tissue injury is a major factor in reoperation after PIP joint fracture dislocation. Specific attention should be paid to persistent subluxation because this may predispose to early arthrosis.

Gepubliceerd: Hand (N Y) 2019 Jul 9;1558944719858429
Impact factor: 0.190; Q4

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11. Treating open lower limb fractures successfully; thoughts and current practice on therapy and centralization in The Netherlands
Oflazoglu K, Hoogendoorn JM, van der Zwaal P, Walbeehm ET, van Enst WA, Holtslag HR, Hofstee D, Plantinga P, Elzinga M, Rakhorst H

Introduction: The British Orthopedic Association (BOA) and British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS) updated the evidence-based guidelines for the treatment and care of open lower limb fractures (BOAST 4). Following this, a Dutch version has been developed. The main points are multidisciplinary care, planning, and treatment of these injuries. Early osteosynthesis (within 7-14 days) combined with soft-tissue coverage results in more efficient care and less complications. AIM: To study the variation in treatment and thoughts among trauma, orthopedic, and plastic surgeons.
Materials and Methods: In this cross-sectional study 94 surgeons (57 trauma, 23 plastic, and 14 orthopedic surgeons) working at 46 centers completed an online questionnaire, consisting of 5 demographic, 14 hospital-related, 8 BOAST 4-related, and 2 centralization-related questions.
Results: There was a strong agreement among surgeons about the best moment for multidisciplinary consultation, which was before initial debridement, while in practice, this often does not occur. All surgeons agreed that the initial debridement should be performed immediately by any surgeon, but not solely by trainees. Plastic surgeons responded that the definitive stabilization and wound cover should not exceed 7 days, while half of the trauma and orthopedic surgeons agreed that it should not exceed 14 days. Finally, most surgeons agreed that Gustilo 3 fractures should be centralized. However, there was disagreement on the need for centralization of Gustilo 2 fractures.
Discussion: Surgeons agree on better and earlier multidisciplinary treatment of open lower limb fractures and the centralization of Gustilo 3 fractures.

Gepubliceerd: Eur J Trauma Emerg Surg 2019;45(1):99-106
Impact factor: 1.781; Q2

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12. How to improve patient safety and quality of care in breast implant surgery? First outcomes from the Dutch Breast Implant Registry (2015-2017)
Spronk PER, Becherer BE, Hommes J, Keuter XHA, Young-Afat DA, Hoornweg MJ, Wouters MWJM, Mureau MAM, Rakhorst HA

Background: Although the use of breast implants is generally considered to be safe, breast implants are associated with short- and long-term complications. To evaluate and improve the quality of breast implant surgery, and increase our knowledge of implant performance, the national Dutch Breast Implant Registry (DBIR) was established in 2015. DBIR is one of the first up-and-running breast implant registries worldwide and follows an opt-out structure. OBJECTIVE: This article provides an overview of the first outcomes and experiences of the DBIR.
Methods: The national coverage of DBIR was studied using data from the Dutch Health and Youth Care Inspectorate. The incidence rate of breast implants was calculated for 2016 and 2017, and patient, device, and surgery characteristics were compared between cosmetic breast augmentations or reconstructive indications. Four infection control, measures were selected to demonstrate the variation in the Dutch clinical practice.
Results: In 2016, 95% of the hospitals and 78% of the private clinics participated in DBIR. Between 2015 and 2017, a total of 15,049 patients and 30,541 breast implants were included. A minimum breast implant incidence rate of 1 per 1,691 women could be determined for 2017. The majority of devices were inserted for a cosmetic indication (85.2%). In general, patient, device, and surgery characteristics differed per indication group. Substantial variation was seen in the use of infection control measures (range 0-100%).
Conclusion: Preliminary results obtained from DBIR show high national participation rates and support further developments toward the improvement of breast implant surgery and patient safety.

Gepubliceerd: J Plast Reconstr Aesthet Surg 2019 Oct;72(10):1607-15
Impact factor: 2.228; Q2

Totale impact factor:
Gemiddelde impact factor:

Aantal artikelen 1e, 2e of laatste auteur: 8
Totale impact factor: 25.734
Gemiddelde impact factor: 3.217

Raad van Bestuur

1. Dark Play of Serious Games: Effectiveness and Features (G4HE2018)
Buijs-Spanjers KR, Hegge HHM, Cnossen F, Hoogendoorn E, Jaarsma DADC, de Rooij SE

Objective: Choosing inappropriate or unethical actions in games is referred to as dark play. For a serious game on delirium for medical students, we aimed to investigate the potential differences between dark play and normal play on game effectiveness regarding abilities in advising care, learning motivation and engagement, and attitude toward delirious patients. Furthermore, we aimed to explore the use of different game features between the two types of play on empathy, self-efficacy, and consequences of care.
Methods: We performed a two-arm randomized controlled trial including an exploratory qualitative approach with 157 medical students, who played the serious game "The Delirium Experience." Participants were randomly allocated to either the dark play or normal play group. Participants had to give three recommendations for taking care of delirious patients, and complete both the Delirium Attitude Scale, and Learning Motivation and Engagement Questionnaire to study game effectiveness. To explore game features, open questions were asked.
Results: We did not find difference between the two types of play in game effectiveness. "Patient's and nurse's perspective" seem to be an important game feature for being able to empathize with a patient in both groups. To support self-efficacy, "practice how to care" and "feedback in the game" were important in both study groups. "Being able to see the importance of good interaction with the patient" was reported important for self-efficacy in the dark play group, whereas this was "seeing the consequences of care" in the normal play group.
Conclusions: There seems to be no change to game effectiveness when providing players the opportunity to use dark play in a serious game. A realistic view of another person's perspective could be an important game feature to increase empathy.

Gepubliceerd: Games Health J 2019 Aug;8(4):301-6
Impact factor: 1.782; Q1

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2. Care trajectories of chronically ill older adult patients discharged from hospital: a quantitative cross-sectional study using health insurance claims data
de Man Y, Atsma F, Jonkers W, de Rooij SEJA, Westert GP, Jeurissen PPT, Groenewoud AS

Background: For older adults, a good transition from hospital to the primary or long-term care setting can decrease readmissions. This paper presents the 6-month post-discharge healthcare utilization of older adults and describes the numbers of readmissions and deaths for the most frequently occurring aftercare arrangements as a starting point in optimizing the post-discharge healthcare organization.
Methods: This cross-sectional study included older adults insured with the largest Dutch insurance company. We described the utilization of healthcare within 180 days after discharge from their first hospital admission of 2015 and the most frequently

occurring combinations of aftercare in the form of geriatric rehabilitation, community nursing, long-term care, and short stay during the first 90 days after discharge. We calculated the proportion of older adults that was readmitted or had died in the 90-180 days after discharge for the six most frequent combinations. We performed all analyses in the total group of older adults and in a sub-group of older adults who had been hospitalized due to a hip fracture.
Results: A total of 31.7% of all older adults and 11.4% of the older adults with a hip fracture did not receive aftercare. Almost half of all older adults received care of a community nurse, whereas less than 5% received long-term home care. Up to 18% received care in a nursing home during the 6 months after discharge. Readmissions were lowest for older adults with a short stay and highest in the group geriatric rehabilitation + community nursing. Mortality was lowest in the total group of older aldults and subgroup with hip fracture without aftercare.
Conclusions: The organization of post-discharge healthcare for older adults may not be organized sufficiently to guarantee appropriate care to restore functional activity. Although receiving aftercare is not a clear predictor of readmissions in our study, the results do seem to indicate that older adults receiving community nursing in the first 90 days less often die compared to older adults with other types of aftercare or no aftercare. Future research is necessary to examine predictors of readmissions and mortality in both older adult patients discharged from hospital.

Gepubliceerd: BMC Geriatr 2019 Oct 15;19(1):266
Impact factor: 2.818; Q1

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3. For which clinical rules do doctors want decision support, and why? A survey of Dutch general practitioners
Medlock S, Eslami S, Askari M, Arts DL, van de Glind EM, Brouwer HJ, van Weert HC, de Rooij SE, Abu-Hanna A

Despite the promise of decision support for improving care, alerts are often overridden or ignored. We evaluated Dutch general practitioners' intention to accept decision support in a proposed implementation based on clinical rules regarding care for elderly patients, and their reasons for wanting or not wanting support. We developed a survey based on literature and structured interviews and distributed it to all doctors who would receive support in the proposed implementation (n = 43), of which 65 percent responded. The survey consisted of six questions for each of 20 clinical rules. Despite concerns about interruption, doctors tended to choose more interruptive forms of support. Doctors wanted support when they felt the rule represented minimal care, perceived a need to improve care, and felt responsible for the action and that they might forget to perform the action; doctors declined support due to feeling that it was unnecessary and due to concerns about interruption.

Gepubliceerd: Health Informatics J 2019 Sep;25(3):1076-90
Impact factor: 2.297; Q2

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4. Assessment instruments in frail older patients; a call for more standardisation

Oud FMM, de Rooij SEJA, Arends AJ, Emmelot-Vonk MH, Melis RJF, Mooijaart SP, Willems HC, van Munster BC

Objective: To determine the frequency and background of the use of assessment instruments for the Comprehensive Geriatric Assessment by clinical geriatricians and internists in geriatric medicine; the secondary aim was to make an inventory of the willingness to standardise the assessment instruments used.
Design: A descriptive questionnaire study. METHOD: In December 2016, we sent out a digital questionnaire (Survey Monkey) to all the hospitals in the Netherlands. Respondents were asked which instruments they used for specific domains of the Comprehensive Geriatric Assessment, what their choice of instruments was based on, if these instruments had added value, and if they were prepared to change the instruments they used.
Results: We received 66 responses (response: 82%). The most frequently-used instruments were: Mini Mental State Examination in combination with the clock drawing test (21%), Geriatric Depression Scale-15 (45%), Katz Index of Independence in Activities of Daily Living-6 (75%), Lawton and Brody (48%), Mini Nutritional Assessment(-short form) (outpatient; 56%) and Short Nutritional Assessment Questionnaire (inpatient: 36%), Experienced Burden Informal Care (46%), Charlson Comorbidity Index (35%), Timed Up and Go (76%), and the Safety Management System (VMS) fall risk question (21%). The most frequently used instruments were used in a large number of hospitals (35-97%).The variation of tests was the greatest in the domains of cognition, malnutrition, and mobility/physical functioning. Many respondents saw the added value of a consensus set of instruments (median: 70%; interquartile range (IQR): 50-86), and most were willing to change the instruments they use (median: 80%; IQR: 65-90).
Conclusion: This inventory shows that the instruments used in most domains were reasonably uniform. Taking the willingness to change into account, a national set of basis instruments seems to be an achievable aim.

Gepubliceerd: Ned Tijdschr Geneeskd 2019 Nov 12;1630;
Impact factor: nvt

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5. Social position and geriatric syndromes among Swedish older people: a population-based study
Rausch C, Liang Y, Bultmann U, de Rooij SE, Johnell K, Laflamme L, Moller J

Background: Older people with a low social position are at higher risk of poor health outcomes compared to those with a higher social position. Whether lower social position also increases the risk of geriatric syndromes (GSs) remains to be determined. This study investigates the association of social position with GSs among older community-dwellers.
Methods: Three consecutive population-based health surveys in 2006, 2010 and 2014 among older community-dwellers (age 65-84 years) in Stockholm County were combined (n = 17,612) and linked with Swedish administrative registry information. Social position was assessed using registry information (i.e. education, country of origin and civil status) and by self-reports (i.e. type of housing and financial stress). GSs were assessed by self-reports of the following conditions: insomnia, urinary incontinence, functional decline, falls, depressive disorder, hearing or vision

problems. Binomial logistic regression analyses were used to estimate the association between social position and GSs after adjusting for age, sex, health status, health behavior and social stress.
Results: The prevalence of GSs was 70.0%, but varied across GSs and ranged from 1.9% for depression to 39.1% for insomnia. Living in rented accommodation, being born outside the Nordic countries, being widowed or divorced were associated with GS presence. Financial stress was most strongly associated with GSs (adjusted odds ratio, 2.59; 95% CI, 2.13-3.15).
Conclusion: GSs are highly prevalent among older Swedish community-dwellers with wide variations across syndromes and strong association with all measures of social position, most strikingly that of experiencing financial stress.

Gepubliceerd: BMC Geriatr 2019 Oct 15;19(1):267
Impact factor: 2.818; Q1

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6. Melatonin, temazepam and placebo in hospitalised older patients with sleeping problems (MATCH): a study protocol of randomised controlled trial
Stenveld F, Bosman S, van Munster BC, Beishuizen SJ, Hempenius L, van d, V, Smidt N, de Rooij SE

Introduction: Hospitalised older patients frequently suffer from inadequate sleep, which can lead to patient distress and delayed recovery from acute illness or surgical procedure. Currently, no evidence-based treatments exist for sleeping problems in hospitalised older patients. Benzodiazepines, such as temazepam, are regularly prescribed by physicians, although they have serious side effects; for older patients in particular. Melatonin is proposed as a safe alternative for sleeping problems in hospitalised older patients, but the efficacy of melatonin is unclear in this population. Therefore, the aim of this study is to investigate the effects of melatonin and temazepam compared with placebo on sleep quality among hospitalised older patients with sleeping problems.
Methods and analysis: This study is a multicentre, randomised, placebo-controlled trial. A total of 663 patients will be randomised in a 1:1:1 fashion to receive either melatonin (n=221), temazepam (n=221) or placebo (n=221). The study population consists of hospitalised patients aged 60 years and older, with new or aggravated sleeping problems for which an intervention is needed. The primary outcome is sleep quality measured with the Leeds Sleep Evaluation Questionnaire (LSEQ). Secondary outcomes include sleep parameters measured with actigraphy and medication-related adverse effects.
Ethisc and dissemination: This study was approved by the Medical Ethics Committee of the Academic Medical Centre Amsterdam, (No 2015_302). Study findings will be disseminated through presentations at professional and scientific conferences and publications in peer-reviewed journals.
Trial registration number: NTR6908; Pre-results.

Gepubliceerd: BMJ Open 2019 May 22;9(5):e025514
Impact factor: 2.376; Q2

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7. Goals of older hospitalised patients: a qualitative descriptive study

van der Kluit MJ, Dijkstra GJ, de Rooij SE

Objectives: Since the population continues ageing and the number of patients with multiple chronic diseases is rising in Western countries, a shift is recommended from disease oriented towards goal-oriented healthcare. As little is known about individual goals and preferences of older hospitalised patients, the aim of this study is to elucidate the goals of a diverse group of older hospitalised patients.
Design: Qualitative descriptive method with open interviews analysed with inductive content analysis.
Setting: A university teaching hospital and a regional teaching hospital.
PARTICIPANTS: Twenty-eight hospitalised patients aged 70 years and older.
Results: Some older hospitalised patients initially had difficulties describing concrete goals, but after probing all were able to state more concrete goals. A great diversity of goals were categorised into wanting to know what the matter is, controlling disease, staying alive, improving condition, alleviating complaints, improving daily functioning, improving/maintaining social functioning, resuming work/hobbies and regaining/maintaining autonomy.
Conclusions: Older hospitalised patients have a diversity of goals in different domains. Discussing goals with older patients is not a common practice yet. Timely discussions about goals should be encouraged because individual goals are not self-evident and this discussion can guide decision making, especially in patients with multimorbidity and frailty. Aids can be helpful to facilitate the discussion about goals and evaluate the outcomes of hospitalisation.

Gepubliceerd: BMJ Open 2019 Aug 5;9(8):e029993
Impact factor: 2.376; Q2

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8. Not feeling ready to go home: a qualitative analysis of chronically ill patients' perceptions on care transitions
Verhaegh KJ, Jepma P, Geerlings SE, de Rooij SE, Buurman BM

Quality problem: Unplanned hospital readmissions frequently occur and have profound implications for patients. This study explores chronically ill patients' experiences and perceptions of being discharged to home and then acutely readmitted to the hospital to identify the potential impact on future care transition interventions.
Initial assessment and implementation: Twenty-three semistructured interviews were conducted with chronically ill patients who had an unplanned 30-day hospital readmission at a university teaching hospital in the Netherlands.
Choice of solution: A constructive grounded theory approach was used for data analysis.
Evaluation: The core category identified was 'readiness for hospital discharge,' and the categories related to the core category are 'experiencing acute care settings' and 'outlook on the recovery period after hospital discharge.' Patients' readiness for hospital discharge was influenced by the organization of hospital care, patients' involvement in decision-making and preparation for discharge. The experienced difficulties during care transitions might have influenced patients' ability to cope with challenges of recovery and dependency on others.

Lessons learned: The results demonstrated the importance of assessing patients' readiness for hospital discharge. Health care professionals are recommended to recognize patients and guide them through transitions of care. In addition, employing specifically designated strategies that encourage patient-centered communication and shared decision-making can be vital in improving care transitions and reduce hospital readmissions. We suggest that health care professionals pay attention to the role and capacity of informal caregivers during care transitions and the recovery period after hospital discharge to prevent possible postdischarge problems.

Gepubliceerd: Int J Qual Health Care 2019 Mar 1;31(2):125-32
Impact factor: 1.829; Q3

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9. Multiple chronic conditions: the need for integrated secondary care
Verhoeff M, Meijer-Smit OM, de Rooij SEJA, van Munster BC

Current hospital-level care is "mostly disease-specific and monodisciplinary-oriented". These three case reports show different journeys that patients with multiple chronic conditions experienced in Dutch secondary outpatient care, and aim to demonstrate why an integrated care approach might be beneficial for this group of patients.

Gepubliceerd: Neth J Med 2019 Aug;77(6):220-3
Impact factor: 0.958; Q3

Totale impact factor: 17.254
Gemiddelde impact factor: 1.917

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 6.534
Gemiddelde impact factor: 1.634

Radiologie

1. Percutaneous Vertebroplasty is no Risk Factor for New Vertebral Fractures and Protects Against Further Height Loss (VERTOS IV)
Firanescu CE, de Vries J, Lodder P, Schoemaker MC, Smeets AJ, Donga E, Juttmann JR, Klazen CAH, Elgersma OEH, Jansen FH, van der Horst I, Blonk M, Venmans A, Lohle PNM

Background: Percutaneous vertebroplasty (PV) is an alternative option to treat pain after an osteoporotic vertebral compression fracture (OVCF). Controversy exists as to whether PV increases the risk of new OVCFs or prevents further vertebral height loss in treated levels. We assessed both during 1-year follow-up in patients with acute OVCF randomised to PV or a sham procedure.
Methods: VERTOS IV is a prospective, multicentre, randomised controlled trial comparing PV with sham therapy in 180 patients. New OVCFs and further vertebral height loss were assessed at 3, 6, and 12 months.
Results: After a median follow-up of 12 months (interquartile range (IQR) = 12-12) 31 new fractures were reported in 15 patients from the PV group and 28 new fractures in 19 patients from the sham group. The occurrence of new vertebral fractures did not significantly differ between the groups (chi(2)(1) = 0.83, p = 0.36, OR = .71, 95%CI = 0.33-1.50). There was no higher fracture risk of adjacent versus distant vertebrae. After sham procedure, further height loss of treated vertebrae occurred more frequently (7 patients (8%) in the PV group and 39 (45%) in the sham group (chi(2)(1) = 28.85, p < 0.001, OR = 9.84, 95%CI = 4.08-23.73)) and was more severe (p < .001) than after PV.
Conclusions: The risk of further vertebral height loss is significantly lower after PV compared to a sham intervention, i.e. PV protects against progressive vertebral height loss. In addition, PV does not increase the risk of new adjacent and distant OVCFs. LEVEL OF EVIDENCE: Level 1a, therapeutic study. ClinicalTrials.gov number, NCT01200277.

Gepubliceerd: Cardiovasc Intervent Radiol 2019 Jul;42(7):991-1000
Impact factor: 1.928; Q3

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2. Optimal respiratory-gated [(18)F]FDG PET/CT significantly impacts the quantification of metabolic parameters and their correlation with overall survival in patients with pancreatic ductal adenocarcinoma
Smeets EMM, Withaar DS, Grootjans W, Hermans JJ, van Laarhoven K, de Geus-Oei LF, Gotthardt M, Aarntzen EHJG

Purpose: Metabolic parameters are increasingly being used to characterize tumors. Motion artifacts due to patient respiration introduce uncertainties in quantification of metabolic parameters during positron emission tomography (PET) image acquisition. The present study investigates the impact of amplitude-based optimal respiratory gating (ORG) on quantification of PET-derived image features in patients with pancreatic ductal adenocarcinoma (PDAC), in correlation with overall survival (OS).
Methods: Sixty-nine patients with histologically proven primary PDAC underwent 2'-deoxy-2'-[(18)F]fluoroglucose ([(18)F]FDG) PET/CT imaging during diagnostic work-

up. Standard image acquisition and reconstruction was performed in accordance with the EANM guidelines and ORG images were reconstructed with a duty cycle of 35%. PET-derived image features, including standard parameters, first- and second-order texture features, were calculated from the standard and corresponding ORG images, and correlation with OS was assessed.
Results: ORG significantly impacts the quantification of nearly all features; values of single-voxel parameters (e.g., SUVmax) showed a wider range, volume-based parameters (e.g., SUVmean) were reduced, and texture features were significantly changed. After correction for motion artifacts using ORG, some features that describe intra-tumoral heterogeneity were more strongly correlated to OS.
Conclusions: Correction for respiratory motion artifacts using ORG impacts the quantification of metabolic parameters in PDAC lesions. The correlation of metabolic parameters with OS was significantly affected, in particular parameters that describe intra-tumor heterogeneity. Therefore, interpretation of single-voxel or average metabolic parameters in relation to clinical outcome should be done cautiously. Furthermore, ORG is a valuable tool to improve quantification of intra-tumoral heterogeneity in PDAC.

Gepubliceerd: EJNMMI Res 2019 Mar 13;9(1):24
Impact factor: 3.000; Q2

Totale impact factor: 4.928
Gemiddelde impact factor: 2.464

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

Radiotherapie

1. Breast-conserving therapy in older patients with breast cancer over three decades: progress or stagnation
Jobsen JJ, Middelburg JG, van der Palen J, Riemersma S, Siemerink E, Struikmans H, Siesling S

Background: The aim of this study was to analyze the distant metastases-free survival (DMFS), and disease-specific survival (DSS) after breast-conserving therapy (BCT) in older patients with breast cancer in a large, population-based, single-center cohort study with long-term follow-up.
Material and methods: Analyses were based on 1,425 women aged 65years and older with breast cancer treated with BCT. Patients were divided in three age categories: 65 - 70years, 71 - 75years, and >75years. The study period extended over 30 years, divided in three decades. Multivariate survival analysis was carried out using Cox regression analysis.
Results: The two youngest age categories showed significant improvements over time in 12-year DMFS and DSS. For women aged 65 - 70years, this improvement was noted in stage I and stage II disease, while for women aged 71 - 75years this was mainly in stage II tumors. Women >75 years of age did not show any improvement over time, regardless of stage.
Conclusion: Among older Dutch women with breast cancer, outcomes with regard to DMFS and DSS after BCT differ between various age categories, showing the least gain in the very old.

Gepubliceerd: J Geriatr Oncol 2019;10(2):330-6
Impact factor: 3.164; Q2

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2. An actualised population-based study on the use of radiotherapy in breast cancer patients in the Netherlands
Schreuder K, Middelburg JG, Aarts MJ, Merkus JWS, Poortmans PMP, Jobsen JJ, Siesling S, Struikmans H

The utilization rate of RT increased from 64.4% in 2011 to 70.3% in 2015. After BCS and mastectomy, 97.3% and 26.1% of the patients received RT, respectively. For patients undergoing BCS and mastectomy, lower age and ER + tumours were associated with higher RT utilisation rates. After mastectomy, also larger tumour sizes, lymph node involvement, grade-2 and 3 tumours and diagnosis in more recent years were associated with higher RT use.

Gepubliceerd: Breast J 2019 Sep;25(5):942-7
Impact factor: 2.433; Q2

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3. Prognostic Impact of Breast-Conserving Therapy Versus Mastectomy of BRCA1/2 Mutation Carriers Compared With Noncarriers in a Consecutive Series of Young Breast Cancer Patients

van den Broek AJ, Schmidt MK, van 't Veer LJ, Oldenburg HSA, Rutgers EJ, Russell NS, Smit VTHB, Voogd AC, Koppert LB, Siesling S, Jobsen JJ, Westenend PJ, van Leeuwen FE, Tollenaar RAEM

Objective: To investigate the effects of different types of surgery on breast cancer prognosis in germline BRCA1/BRCA2 mutation carriers compared with noncarriers.
Summary of background data: Although breast-conserving therapy (breast-conserving surgery followed by radiotherapy) has been associated with more local recurrences than mastectomy, no differences in overall survival have been found in randomized trials performed in the general breast cancer population. Whether breast-conservation can be safely offered to BRCA1/2 mutation carriers is debatable.
Methods: The study comprised a cohort of women with invasive breast cancer diagnosed <50 years and treated between 1970 and 2003 in 10 Dutch centers. Germline DNA for BRCA1/2 testing of most-prevalent mutations (covering approximately 61%) was mainly derived from paraffin-blocks. Survival analyses were performed taking into account competing risks.
Results: In noncarriers (N = 5820), as well as in BRCA1 (N = 191) and BRCA2 (N = 70) mutation carriers, approximately half of the patients received breast-conserving therapy. Patients receiving mastectomy followed by radiotherapy had prognostically worse tumor characteristics and more often received systemic therapy. After adjustment for these potential confounders, patients who received breast-conserving therapy had a similar overall survival compared with patients who received mastectomy, both in noncarriers (hazard ratio [HR] = 0.95, confidence interval [CI] = 0.85-1.07, P = 0.41) and BRCA1 mutation carriers (HR = 0.80, CI = 0.42-1.51, P = 0.50). Numbers for BRCA2 were insufficient to draw conclusions. The rate of local recurrences after breast-conserving therapy did not differ between BRCA1 carriers (10-year risk = 7.3%) and noncarriers (10-year risk = 7.9%).
Conclusion: Our results, together with the available literature, provide reassurance that breast-conserving therapy is a safe local treatment option to offer to BRCA1 mutation carriers with invasive breast cancer.

Gepubliceerd: Ann Surg 2019 Aug;270(2):364-72
Impact factor: 9.476; Q1

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4. Effect of physical exercise on cognitive function and brain measures after chemotherapy in patients with breast cancer (PAM study): protocol of a randomised controlled trial
Witlox L, Schagen SB, de Ruiter MB, Geerlings MI, Peeters PHM, Koevoets EW, van der Wall E, Stuiver M, Sonke G, Velthuis MJ, van der Palen J, Jobsen JJ, May AM, Monninkhof EM

Introduction: After treatment with chemotherapy, many patients with breast cancer experience cognitive problems. While limited interventions are available to improve cognitive functioning, physical exercise showed positive effects in healthy older adults and people with mild cognitive impairment. The Physical Activity and Memory study aims to investigate the effect of physical exercise on cognitive functioning and brain measures in chemotherapy-exposed patients with breast cancer with cognitive problems.

Methods and analytics: One hundred and eighty patients with breast cancer with cognitive problems 2-4 years after diagnosis are randomised (1:1) into an exercise intervention or a control group. The 6-month exercise intervention consists of twice a week 1-hour aerobic and strength exercises supervised by a physiotherapist and twice a week 1-hour Nordic or power walking. The control group is asked to maintain their habitual activity pattern during 6 months. The primary outcome (verbal learning) is measured at baseline and 6 months. Further measurements include online neuropsychological tests, self-reported cognitive complaints, a 3-tesla brain MRI, patient-reported outcomes (quality of life, fatigue, depression, anxiety, work performance), blood sampling and physical fitness. The MRI scans and blood sampling will be used to gain insight into underlying mechanisms. At 18 months online neuropsychological tests, self-reported cognitive complaints and patient-reported outcomes will be repeated.
Ethisc and dissemination: Study results may impact usual care if physical exercise improves cognitive functioning for breast cancer survivors.
Trial registration number: NTR6104.

Gepubliceerd: BMJ Open 2019 Jun 20;9(6):e028117
Impact factor: 2.376; Q2

Totale impact factor: 17.449
Gemiddelde impact factor: 4.326

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 3.164
Gemiddelde impact factor: 3.164

Reumatologie

1. Physical and Emotional Burden of Rheumatoid Arthritis: Data from RA Matters, a Web-Based Survey of Patients and Healthcare Professionals
Alten R, van de Laar M, De Leonardis F, Tietz N, Guerreiro M, van Vollenhoven R

Introduction: This survey assessed the impact of rheumatoid arthritis (RA) on the lives of patients based on the perceptions of both patients and healthcare professionals (HCPs).
Methods: This is a cross-sectional survey of patients with RA. Data were collected from patients and HCPs who manage RA using a structured, closed-ended questionnaire in their local language. Respondents for the survey were recruited from survey panels of verified unique responses. The survey focused on the impact of disease on four domains: daily activities, relationships, work and aspirations.
Results: Overall, 1231 adult patients with RA and 270 rheumatologists or other HCPs were surveyed between November 2016 and February 2017. Almost one in three patients believed that the impact of RA is not well understood by people without the disease. Fifty-eight percent [95% confidence interval (CI) 55-61%] of patients felt frustrated when they were unable to undertake or complete daily activities because of their disease. Fifty-seven percent (95% CI 54-60%) of patients wished to be able to accept their life with RA. Forty-three percent (95% CI 40-46%) of patients hoped that the physical impact of RA will be better understood in future. Forty percent (95% CI 37-43%) of patients were forced to take long-term leave/retirement or experienced slow career progression since being diagnosed with RA. Twenty-three percent (95% CI 21-25%) of patients had difficulties in taking care of personal grooming, whereas 8% (95% CI 6-10%) of patients reported that RA ruined their life. Similar responses were observed among HCPs.
Conclusion: Patients and HCPs feel that the physical and emotional impact of RA is not well understood by people without the disease. In RA treatment decisions, patients' personal goals and patient-reported outcomes should be taken into consideration along with clinical targets.
Funding: Eli Lilly and Company (Indianapolis, IN, USA).

Gepubliceerd: Rheumatol Ther 2019 Dec;6(4):587-97
Impact factor: 0; nvt

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2. Trajectories of Physical Work Capacity in Early Symptomatic Osteoarthritis of Hip and Knee: Results from the Cohort Hip and Cohort Knee (CHECK) Study
Bieleman HJ, Stewart R, Reneman MF, van Ittersum WM, van der Schans CP, Drossaers-Bakker KW, Oosterveld FGJ

Purpose: To evaluate the 5-year course of physical work capacity of participants with early symptomatic osteoarthritis (OA) of the hip and/or the knee; to identify trajectories and explore the relationship between trajectories and covariates.
Methods: In a prospective cohort study, physical work capacity was measured at baseline, using a test protocol (functional capacity evaluation) consisting of work-related physical activities. Participants were invited to participate in 1, 2 and 5 year follow-up measurements. Multilevel analysis and latent classes analysis were

performed, in models with test performances as dependent variables and age, sex, work status, self-reported function (Western Ontario McMasters Arthritis Scale-WOMAC), body mass index (BMI) and time as independent variables. Multiple imputation was used to control for the influence of missing data.
Results: At baseline and after 1, 2 and 5 years there were 96, 64, 61 and 35 participants. Mean (SD) age at baseline was 56 (4.9) years, 84% were females. There was no statistically significant change in test performances (lifting low and high, carrying, static overhead work, repetitive bending, repetitive rotations) between the 4 measurements. Male sex, younger age and better self-reported function were statistically significant ($p < 0.05$) determinants of higher performance on most of the tests; having a paid job, BMI and progression of time were not. Three trajectories were identified: 'weak giving way', 'stable and able', and 'strong with decline'.
Discussion: In subgroups of participants with early symptomatic OA, determined by age, sex and self-reported function, physical work capacity seems to be a stable characteristic over 5 years.

Gepubliceerd: J Occup Rehabil 2019 Sep;29(3):483-92
Impact factor: 2.242; Q1

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3. Predictors of biologic-free disease control in patients with rheumatoid arthritis after stopping tumor necrosis factor inhibitor treatment
Ghiti Moghadam M, Lamers-Karnebeek FBG, Vonkeman HE, Ten Klooster PM, Tekstra J, van Schaeybroeck B, Klaasen R, van Onna M, Bernelot Moens HJ, Visser H, Schilder AM, Kok MR, Landewe RBM, van Riel PLCM, van de Laar MAFJ, Jansen TL

Background: The aim of this study was to identify predictors of prolonged disease control after discontinuation of tumor necrosis factor inhibitor (TNFi) treatment in patients with rheumatoid arthritis (RA).
Methods: Post-hoc analysis of 439 RA patients (67.3% rheumatoid factor positive) with longstanding RA in remission or with stable low disease activity, randomized to stopping TNFi treatment in the multicenter POET trial. Prolonged acceptable disease control was defined as not restarting TNFi treatment within 12 months after stopping. Baseline demographic and disease-related variables were included in univariate and multivariate logistic regression analysis for identifying predictors of relapse.
Results: One year after baseline, 220 patients (50.1%) had not restarted TNFi treatment. Use of an anti-TNF monoclonal antibody (versus a receptor antagonist, OR = 2.41; 95% CI: 1.58-3.67), </=10 yrs. disease duration (OR = 2.15; 95% CI: 1.42-3.26) and low or moderate multi-biomarker disease activity (MBDA) scores (OR = 2.00; 95% CI: 1.10-3.64) at baseline were independently predictive of successful TNFi discontinuation (area under the receiver operating characteristic curve = 0.66; 95% CI: 0.61-0.71). Results were similar when using no physician-reported flare as the criterion. TNFi-free survival was significantly different for patient groups based on the number of predictors present, ranging from 21.4% of patients with no predictor present to 66.7% of patients with all three predictors present.
Conclusion: Patients using an anti-TNF monoclonal antibody, with shorter disease duration and low or moderate baseline MBDA score are most likely to achieve prolonged disease control after TNFi discontinuation. Trial registration: Netherlands Trial Register NTR3112, 21 October 2011.

Gepubliceerd: BMC Rheumatol 2019;3:3
Impact factor: 0; nvt

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4. A systematic literature review of patient-reported outcome measures used in gout: an evaluation of their content and measurement properties
Janssen CA, Oude Voshaar MAH, Ten Klooster PM, Jansen TLTA, Vonkeman HE, van de Laar MAFJ

Background: Gout is a common, monosodium urate crystal-driven inflammatory arthritis. Besides its clinical manifestations, patients often also suffer from pain, physical impairment, emotional distress and work productivity loss, as a result of the disease. Patient-reported outcome measures (PROMs) are commonly used to assess these consequences of the disease. However, current instrument endorsements for measuring such outcomes in acute and chronic gout clinical settings are based on limited psychometric evidence. The objective of this systematic literature review was to identify currently available PROMs for gout, and to critically evaluate their content and psychometric properties, in order to evaluate the current status regarding PROMs for use in gout patients.
Methods: Systematic literature searches were performed in the PubMed and EMBASE databases. The methodological quality of included papers was appraised using the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist, and evaluation of measurement properties (reliability, responsiveness, construct validity, floor and ceiling effects) was done in accordance with published quality criteria. Item content was appraised by linking health concepts to the International Classification of Functioning Disability and Health (ICF) framework.
Results: In total, 13 PROMs were identified, of which three were targeted specifically at gout patients. The majority of the PROMs were rated positively for content validity. For most instruments, limited evidence was available for construct validity and reliability. Instruments to assess pain scored well on responsiveness and floor and ceiling effects, but not much is known about their reliability in gout.
Conclusions: The physical functioning subscale of the SF-36v2 (Short Form-36 item version 2) is the only PROM that had sufficient supporting evidence for all its psychometric properties. Many of the commonly used PROMs in gout are currently not yet well supported and more studies on their measurement properties are needed among both acute and chronic gout populations.

Gepubliceerd: Health Qual Life Outcomes 2019 Apr 11;17(1):63
Impact factor: 2.318; Q2

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5. Development and validation of a patient-reported gout attack intensity score for use in gout clinical studies
Janssen CA, Oude Voshaar MAH, Ten Klooster PM, Vonkeman HE, van de Laar MAFJ

Objective: Inflammation-related symptoms such as pain, swelling and tenderness of the affected joint are frequently assessed using 5-point diary rating scales in gout

clinical trials. Combining these into a single gout attack symptom intensity score may be a useful summary measure for these data, which is potentially more responsive to change compared with the individual components. The objective of this study was to develop a patient-reported gout flare intensity score, the Gout Attack Intensity Score (GAIS), for use in clinical studies, that includes components for gout-related pain, swelling and tenderness.
Methods: Data from a randomized controlled trial comparing anakinra to standard of care for the treatment of acute gout attacks were used for this study. A 7-day flare diary was completed by patients, including questions relating to intensity of pain, swelling and tenderness (5-point rating scales). Scalability of these items was assessed using Mokken Scale Analysis, and reliability using greatest lower bound reliability coefficients. Known-groups validity was evaluated, as well as the responsiveness to change and the presence of floor and ceiling effects.
Results: Scalability of the single items was supported, and GAIS scores were reliable (greatest lower bound >0.80). GAIS scores demonstrated responsiveness to change with high effect sizes (>0.8), and discriminated better between responders and non-responders compared with its single-item components. No floor and ceiling effects were found.
Conclusion: The GAIS seems to be a reliable and responsive instrument for assessing patient-reported gout attack intensity that may be used in gout clinical studies.

Gepubliceerd: Rheumatology (Oxford) 2019 Nov 1;58(11):1928-34
Impact factor: 5.149; Q1

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6. Prognostic factors associated with early gout flare recurrence in patients initiating urate-lowering therapy during an acute gout flare
Janssen CA, Oude Voshaar MAH, Ten Klooster PM, Vonkeman HE, van de Laar MAFJ

Lowering serum urate levels below the threshold for crystal formation with urate-lowering therapy (ULT) has been associated with a lower risk for gout flare reoccurrences. However, gout patients on ULT still commonly suffer from recurring gout flares. The purpose of this study was to explore prognostic factors associated with gout flare recurrence within the first 3 months, in gout patients starting ULT during an acute gout flare. Post-hoc analysis of trial data on acute gout patients randomized to either gout flare standard of care or anakinra treatment were used, including baseline demographic, laboratory, clinical, and patient-reported variables, as well as 3-month follow-up data on gout flare recurrences. Only patients starting ULT at baseline were included. Using variable selection based on clinical relevance, univariate, and multivariate binary logistic regression analyses were done to examine predictors of gout flare reoccurrence. A total of 75 patients were included in this study, of which 36 (48%) experienced a gout flare </= 3 months post baseline. The multivariate regression analysis revealed that CRP levels > 30 mg/L (OR 9.47) and lack of prophylaxis when starting ULT (OR 11.56) were independently associated with gout flare recurrence. Similar results were found for the univariate regression analyses. Our results show that CRP levels > 30 mg/L and lack of prophylaxis when starting ULT were prognostic factors for early gout flare reoccurrence in patients starting ULT during an acute gout flare. KEY POINTS: * Gout flare recurrences were

common within the first 3 months after starting urate-lowering therapy in gout patients. * Intake of prophylaxis when starting ULT had a strong protective effect on gout flare recurrences. * C-reactive protein level > 30 mg/L was an additional prognostic factor for early (</= 3 months) gout flare reoccurrence in patients starting ULT during an acute gout flare.

Gepubliceerd: Clin Rheumatol 2019 Aug;38(8):2233-9
Impact factor: 2.293; Q3

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7. International Consortium for Health Outcome Measurement (ICHOM)Set of Outcomes that Matter to People Living with Inflammatory Arthritis Consensus from an international Working Group

Oude Voshaar MAH, Das GZ, Bijlsma JWJ, Boonen A, Chau J, Courvoisier DS, Curtis JR, Ellis B, Ernestam S, Gossec L, Hale C, Hornjeff J, Leung KYY, Lidar M, Mease P, Michaud K, Mody GM, Ndosi M, Opava CH, Pinheiro GRC, Salt M, Soriano ER, Taylor WJ, Voshaar MJH, Weel AEAM, de Wit M, Wulffraat N, van de Laar MAFJ, Vonkeman HE

Background: The implementation of value based healthcare (VBHC) in inflammatory arthritis (IA) requires a standardized set of modifiable outcomes and risk-adjustment variables that is feasible to implement worldwide.
Methods: The International Consortium for Health Outcomes Measurement (ICHOM) assembled a multidisciplinary working group, consisting of 24 experts from six continents, including six patient representatives, to develop a Standard Set of outcomes for IA. The process followed a structured approach using a modified Delphi process to reach consensus on 1) conditions covered by the set, 2) outcome domains, 3) outcome measures, 4) risk-adjustment variables. Consensus on decision areas two to four were supported by systematic literature reviews and consultation of experts.
Results: The ICHOM IA Standard Set covers patients with rheumatoid arthritis (RA), axial spondyloarthritis, psoriatic arthritis and juvenile idiopathic arthritis (JIA). We recommend that the following outcomes be collected at least annually: pain, fatigue, activity limitations, overall physical and mental health impact, work/school/housework ability and productivity, disease activity, and serious adverse events. Validated measures for patient-reported outcomes were endorsed, and linked to common reporting metrics. Age, sex at birth, educational level, smoking status, comorbidities, time since diagnosis, and rheumatoid factor and anti-citrullinated protein antibody lab testing for RA and JIA should be collected as risk-adjustment variables.
Conclusion: We present the ICHOM IA Standard Set of outcomes that enables healthcare providers to implement the value based healthcare framework and enable comparison of outcomes important to patients with IA. This article is protected by copyright. All rights reserved.

Gepubliceerd: Arthritis Care Res (Hoboken) 2019;71(12):1556-65
Impact factor: 4.530; Q2

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8. Psychometric properties and cross-language equivalence of the revised Bristol Rheumatoid Arthritis Fatigue and the Rheumatoid Arthritis Impact of Disease scales in rheumatoid arthritis
Oude Voshaar MAH, Bode C, Hewlett S, Kirwan J, Gossec L, van de Laar MAFJ

Objective: To assess psychometric properties and cross-language measurement equivalence of six versions of the Bristol Rheumatoid Arthritis Fatigue Scale (BRAF-MDQ) and the Rheumatoid Arthritis Impact of Disease Score (RAID in rheumatoid arthritis (RA).
Methods: Both questionnaires were completed by French (n = 206), German (n = 206), Dutch (n = 317), Spanish (n = 157), Swedish (n = 170) and UK (n = 210) RA patients. The presence of cross-language differential item functioning (DIF) was examined using the generalized partial credit model. The impact of DIF on the item and total scores was examined by comparing DIF unadjusted and DIF adjusted expected item and scale scores. IRT-based methods were used to assess psychometric properties of the instruments.
Results: 11 of the 20 BRAF-MDQ (55%) and 4 of the 7 RAID items (57%) exhibited significant DIF in at least one of the six countries. The mean number of items with DIF per country was 2.6 for BRAF-MDQ and 1.1 for RAID. However, the impact of DIF on the total RAID and BRAF-MDQ scores, as well as the BRAF subscales, was found to be negligible at the group level. Only for the BRAF physical subscale was there evidence of minor DIF. Marginal reliabilities of BRAF-MDQ (0.93) and RAID (0.89) were excellent, and precise scores could be obtained across the spectrum of disease impact and fatigue scores measured by these PROMs.
Conclusion: This study supports the cross-language measurement equivalence of BRAF-MDQ and RAID and provides further support for the psychometric properties of these measures in RA.

Gepubliceerd: Qual Life Res 2019 Sep;28(9):2543-52
Impact factor: 2.488; Q2

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9. Taking the patient and the patient's perspective into account to improve outcomes of care of patients with musculoskeletal diseases
Oude Voshaar MAH, van de Laar MAFJ

Patient-reported outcome measures are commonly used in the assessment of patients with musculoskeletal diseases. The present review provides an overview of historic and recent developments, including core set recommendations for assessing patient-reported outcomes in patients with fibromyalgia, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. The evidence supporting commonly used patient-reported outcomes measures is reviewed. Furthermore, various methodological approaches that can be utilized to evaluate validity and measurement precision of patient reported outcomes are introduced. Commonly used methods based on the classical test theory as well as modern approaches based on item response theory will be discussed. The review finally describes the increasing use of item response theory-based approaches used in patient-reported outcomes assessment in the musculoskeletal diseases.

Gepubliceerd: Best Pract Res Clin Rheumatol 2019 Jun;33(3):101436

Impact factor: 3.016; Q3

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10. Towards standardized patient reported physical function outcome reporting: linking ten commonly used questionnaires to a common metric
Oude Voshaar MAH, Vonkeman HE, Courvoisier D, Finckh A, Gossec L, Leung YY, Michaud K, Pinheiro G, Soriano E, Wulfraat N, Zink A, van de Laar MAFJ

Objectives: Outcomes obtained using different physical function patient reported outcome measures (PROMs) are difficult to compare. To facilitate standardization of physical function outcome measurement and reporting we developed an item response theory (IRT) based standardized physical function score metric for ten commonly used physical function PROMs.
Methods: Data of a total of 16,386 respondents from representative cohorts of patients with rheumatic diseases as well as the Dutch general population were used to map the items of ten commonly used physical function PROMs on a continuous latent physical function variable. The resulting IRT based common metric was cross-validated in an independent dataset of 243 patients with gout, osteoarthritis or polymyalgia in which four of the linked PROMs were administered.
Results: Our analyses supported that all 97 items of the ten included PROMs relate to a single underlying physical function variable and that responses to each item could be described by the generalized partial credit IRT model. In the cross-validation analyses we found congruent mean scores for four different PROMs when the IRT based scoring procedures were used.
Conclusions: We showed that the standardized physical function score metric developed in this study can be used to facilitate standardized reporting of physical function outcomes for ten commonly used make physical function PROMs.

Gepubliceerd: Qual Life Res 2019;28(1):187-97
Impact factor: 2.488; Q2

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11. Association between pain phenotype and disease activity in rheumatoid arthritis patients: a non-interventional, longitudinal cohort study
Ten Klooster PM, de Graaf N, Vonkeman HE

Background: In well-controlled rheumatoid arthritis (RA) without significant joint damage, a substantial proportion of patients complain of persistent pain. Previous studies have identified different pain phenotypes in RA, in which non-nociceptive pain phenotypes are associated with higher concurrent disease activity scores. In this longitudinal study, we explored associations between pain phenotypes and long-term disease activity outcome in RA patients. Secondly, we explored whether pain phenotype is associated with comorbid conditions.
Methods: One hundred eighty established RA patients were classified with a nociceptive (61%) or a non-nociceptive (39%) pain phenotype, based on their responses to the painDETECT-questionnaire. Two years of clinical follow-up data on disease activity outcomes were collected. Information on comorbid diseases was derived from electronic patient files.
Results: Patients with a non-nociceptive pain phenotype showed higher mean disease activity scores (DAS28, 2.57; 95% CI, 2.37-2.77 vs. 2.11; 95% CI, 1.94-2.27;

p < 0.001) and a twofold lower chance of achieving sustained DAS28 remission (OR = 0.49; 95% CI, 0.26-0.92; p = 0.020). Only the tender joint count and patient global health significantly differed between the pain phenotype groups. Patients with a non-nociceptive pain phenotype had more often been diagnosed with concurrent fibromyalgia (9.9% vs. 0.9%; p = 0.007) and other pain-associated comorbid diseases (52.1% vs. 35.8%; p = 0.030) compared with patients with a nociceptive pain phenotype.
Conclusion: This longitudinal study showed consistently worse long-term disease activity outcomes in RA patients with a non-nociceptive pain phenotype which appeared to be mainly due to differences in the subjective components of the disease activity score.
Trial Registration: The DREAM cohort study is registered in the Netherlands Trial Register: NTR578.

Gepubliceerd: Arthritis Res Ther 2019 Nov 29;21(1):257
Impact factor: 4.148; Q2

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12. Long-term clinical, functional, and cost outcomes for early rheumatoid arthritis patients who did or did not achieve early remission in a real-world treat-to-target strategy
Ten Klooster PM, Oude Voshaar MAH, Fakhouri W, de la Torre I, Nicolay C, van de Laar MAFJ

Objective: To retrospectively compare the long-term clinical, functional, and cost outcomes for early RA patients (symptoms < 1 year) who did or did not achieve early remission in a treat-to-target strategy.
Method: Five-year data of 471 patients included in the DREAM remission induction cohort were used. Patients were treated according to a pre-specified 28-joint Disease Activity Score (DAS28) remission driven step-up treatment strategy starting with methotrexate, addition of sulfasalazine, and exchange of sulfasalazine for biological medication in case of failure. Two- and 3-year healthcare costs were available for selected subsamples of patients only.
Results: DAS28 remission was achieved in 27.7%, 38.2%, and 51.6% of patients at 2, 3, and 6 months, respectively. Achieving DAS28 remission at 2, 3, or 6 months was consistently associated with significantly lower DAS28 and Health Assessment Questionnaire-Disability scores at 1, 3, and 5 years of follow-up (all P values < 0.02). Patients in remission at 2, 3, or 6 months also had significantly lower medication costs per patient over the first 2 and 3 years of treatment, mainly due to lower biologic use, but differences in total healthcare resource costs (hospital admissions plus consultations) were less pronounced. Mean total medication and total healthcare resource costs at 3 years were euro1131 and euro1757 for patients in remission at 6 months vs. euro7533 (P < 0.01) and euro2202 (P = 0.09) for those not in remission.
Conclusion: Achieving early remission was associated with beneficial clinical outcomes for early RA patients and lower costs in the long term. Key Points * Previous studies in rheumatoid arthritis patients have demonstrated that early good response is associated with sustained remission and better long-term clinical outcomes. * This study extents these findings by examining the long-term benefits of achieving early remission on clinical, patient-reported, and economic outcomes in a real-world cohort of patients with very early rheumatoid arthritis treated according to

treat-to-target principles. * The findings of this study clearly demonstrate that aiming for early remission in rheumatoid arthritis patients is beneficial in the long-term in terms of better clinical and functional outcomes and lower healthcare costs.

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13. Radiographic progression can still occur in individual patients with low or moderate disease activity in the current treat-to-target paradigm: real-world data from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry
Ten Klooster PM, Versteeg LGA, Oude Voshaar MAH, de la Torre I, De Leonardis F, Fakhouri W, Zaremba-Pechmann L, van de Laar M

Background: The aim of this retrospective study was to examine the longitudinal association between disease activity and radiographic damage in a cohort of patients with early RA (symptom onset < 1 year) treated according to treat-to-target (T2T) therapy.
Methods: Baseline to 3-year follow-up data were used from patients included in the DREAM remission induction cohort. Patients received protocolized T2T treatment, aimed at 28-joint disease activity score-erythrocyte sedimentation rate (DAS28-ESR) remission. Disease activity (DAS28-ESR and C-reactive protein, CRP) were assessed at least every 3 months; X-rays of the hand and feet at inclusion, 6 months, and 1, 2, and 3 years were scored using modified Sharp/van der Heijde scoring (SHS). Between and within-person associations between time-integrated disease activity and radiographic progression over time were examined.
Results: A subset of 229 out of 534 included patients were available for analysis. At the between-patient level, time-integrated DAS28-ESR scores were not significantly correlated with progression at the 6 month and 2-year follow-up and only weakly at the 1-year (Pearson's correlation coefficient $r = 0.17$, $P < 0.05$) and 3-year follow-up ($r = 0.21$, $P < 0.05$). Individual slopes of the relationship between DAS28-ESR and progression scores in each time interval were significantly correlated over time and the slope of the first 6 months was moderately associated with this slope at later time points (r between 0.39 and 0.59; P values < 0.001). Between 15.9 to 22.7% and 16.7 to 38.5% of patients with low and moderate time-integrated disease activity, respectively, experienced relevant (DeltaSHS >/= 3) radiographic progression at the different time intervals. Analyses using CRP showed similar results.
Conclusions: In early RA patients treated according to T2T, radiographic progression appears to be an individually determined disease process, driven by factors other than consistent high disease activity. For individual patients, the intra-patient relation between disease activity and cumulative radiographic damage during the first 6 months is a good indicator for this relation in later years.
Trial Registration: Netherlands Trial Register NTR578, 12 January 2006.

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Impact factor: 4.148; Q2

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14. Development and preliminary evaluation of a short self-report measure of generalized pain hypersensitivity

van Bemmel PF, Oude Voshaar MA, Klooster PMT, Vonkeman HE, van de Laar MA

Purpose: Generalized pain hypersensitivity is frequently observed in chronic pain conditions. Currently, identification is based on expert clinical opinion, and in very few cases combined with quantitative sensory testing. The objectives of this study were to develop and evaluate a short self-report measure of generalized pain hypersensitivity: a generalized pain questionnaire (GPQ).
Methods: Items for the GPQ were developed based on a literature review, followed by an interview study with ten rheumatic patients with suspected pain hypersensitivity. We examined the psychometric properties of the preliminary items in a sample of 212 outpatients suffering from either fibromyalgia (FM; n=98) or rheumatoid arthritis (n=114). Additionally, self-reported data were gathered on sociodemographics, fibromyalgia-survey criteria, health status, and neuropathic-like pain features.
Results: Mokken-scale analyses demonstrated a unidimensional seven-item scale with strong homogeneity (H=0.65) and high reliability (r=0.90). Correlations between total GPQ scores and relevant external measures, such as the FM-survey criteria and neuropathic-like pain features, were consistent with a priori expectations, supporting its external construct validity. Furthermore, the GPQ had good accuracy in distinguishing between patients with FM (generally assumed to be the result of central nervous system hypersensitization) and patients with RA (assumed to result mostly in local nociceptive or inflammatory pain), with an area under the receiver-operating characteristic curve of 0.89. A cutoff value >10 had the highest combination of sensitivity (82.7%) and specificity (77.2%).
Conclusion: The GPQ is psychometrically sound and appears promising for measuring the presence and severity of generalized pain hypersensitivity in chronic pain patients.

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Impact factor: 2.236; Q3

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15. Cost-effectiveness of different treat-to-target strategies in rheumatoid arthritis: results from the DREAM registry
van de Laar CJ, Oude Voshaar MAH, Vonkeman HE

Background: Adjusting medication of patients with rheumatoid arthritis (RA) until predefined disease activity targets are met, i.e. Treat-to-Target (T2T), is the currently recommended treatment approach. However, not much is known about long-term cost-effectiveness of different T2T strategies.We model the 5-year costs and effects of a step-up approach (MTX mono - > MTX + csDMARD combination - > Adalimumab - > second anti-TNF) and an initial combination therapy approach (MTX + csDMARD - > MTX + csDMARD higher dose - > anti-TNFs) from the healthcare and societal perspectives, by adapting a previously validated Markov model.
Methods: We constructed a Markov model in which 3-monthly transitions between DAS28-defined health states of remission (≤2.6), low (2.6 < DAS28 ≤ 3.2), moderate (3.2 < DAS28 ≤ 5.1), and high disease activity (DAS28 > 5.1) were simulated. Modelled patients proceeded to subsequent treatments in case of non-remission at each (3-month) cycle start. In case of remission for two consecutive cycles medication was tapered, until medication-free remission was achieved. Transition probabilities for individual treatment steps were estimated using data of Dutch

Rheumatology Monitoring registry Remission Induction Cohort I (step-up) and II (initial combination). Expected costs, utility, and ICER after 5 years were compared between the two strategies. To account for parameter uncertainty, probabilistic sensitivity analysis was employed through Gamma, Normal, and Dirichlet distributions. All utilities, costs, and transition probabilities were replaced by fitted distributions.
Results: Over a 5-year timespan, initial combination therapy was less costly and more effective than step-up therapy. Initial combination therapy accrued €16,226.3 and 3.552 QALY vs €20,183.3 and 3.517 QALYs for step-up therapy. This resulted in a negative ICER, indicating that initial combination therapy was both less costly and more effective in terms of utility gained. This can be explained by higher (±5%) remission percentages in initial combination strategy at all time points. More patients in remission generates less healthcare and productivity loss costs and higher utility. Additionally, higher remission percentages caused less bDMARD use in the initial combination strategy, lowering overall costs.
Conclusion: Initial combination therapy was found favourable over step-up therapy in the treatment of Rheumatoid Arthritis, when considering cost-effectiveness. Initial combination therapy resulted in more utility at a lower cost over 5 years

BMC Rheumatol 2019;3:16
Impact factor: 0; nvt

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16. Preferences of patients with rheumatoid arthritis regarding disease-modifying antirheumatic drugs: a discrete choice experiment
van Heuckelum M, Mathijssen EG, Vervloet M, Boonen A, Hebing RC, Pasma A, Vonkeman HE, Wenink MH, van den Bemt BJ, van Dijk L

Background: Although patients have different treatment preferences, these individual preferences could often be grouped in subgroups with shared preferences. Knowledge of these subgroups as well as factors associated with subgroup membership supports health care professionals in the understanding of what matters to patients in clinical decision-making. Objectives: To identify subgroups of patients with rheumatoid arthritis (RA) based on their shared preferences toward disease-modifying antirheumatic drugs (DMARDs), and to identify factors associated with subgroup membership.
Methods: A discrete choice experiment to determine DMARD preferences of adult patients with RA was designed based on a literature review, expert recommendations, and focus groups. In this multicenter study, patients were asked to state their preferred choice between two different hypothetical treatment options, described by seven DMARD characteristics with three levels within each characteristic. Latent class analyses and multinomial logistic regressions were used to identify subgroups and the characteristics (patient characteristics, disease-related variables, and beliefs about medicines) associated with subgroup membership.
Results: Among 325 participating patients with RA, three subgroups were identified: an administration-driven subgroup (45.6%), a benefit-driven subgroup (29.7%), and a balanced subgroup (24.7%). Patients who were currently using biologic DMARDs were significantly more likely to belong to the balanced subgroup than the administration-driven subgroup (relative risk ratio (RRR): 0.50, 95% CI: 0.28-0.89). Highly educated patients were significantly more likely to belong to the benefit-driven

subgroup than the balanced subgroup (RRR: 11.4, 95% CI: 0.97-133.6). Patients' medication-related concerns did not contribute significantly to subgroup membership, whereas a near-significant association was found between patients' beliefs about medication necessity and their membership of the benefit-driven subgroup (RRR: 1.12, 95% CI: 1.00-1.23).
Conclusion: Three subgroups with shared preferences were identified. Only biologic DMARD use and educational level were associated with subgroup membership. Integrating patient's medication preferences in pharmacotherapy decisions may improve the quality of decisions and possibly medication adherence.

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Impact factor: 2.097; Q2

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17. Development, usability and acceptability of an integrated eHealth system for spondyloarthritis in the Netherlands (SpA-Net)
Webers C, Beckers E, Boonen A, van Eijk-Hustings Y, Vonkeman H, van de Laar M, van Tubergen A

Objective: To develop and test the usability and acceptability of a disease-specific integrated electronic health (eHealth) system for spondyloarthritis (SpA) in the Netherlands ('SpA-Net').
Methods: SpA-Net was developed in four phases. First, content and design were discussed with experts on SpA and patients. Second, the database, electronic medical record (EMR) and quality management system were developed. Third, multiple rounds of testing were performed. Fourth, the eHealth system was implemented in practice and feasibility was tested among patients through semistructured focus interviews (n=16 patients) and among care providers through feedback meetings (n=11 rheumatologists/fellows and 5 nurses).
Results: After completion of the first three steps of development in 2015, SpA-Net was implemented in 2016. All patients included have a clinical diagnosis of SpA. Information on domains relevant to clinical record-keeping is prospectively collected at routine outpatient consultations and readily available to care providers, presented in a clear dashboard. Patients complete online questionnaires prior to outpatient visits. In February 2019, 1069 patients were enrolled (mean [SD] age 54.9 [14.1] years, 52.4% men). Patients interviewed (n=16) considered SpA-Net an accessible system that was beneficial to disease insight and patient-physician communication, and had additional value to current care. Care providers appreciated the additional information for (preparing) consultations. Barriers were the initial time required to adopt the EMR and the quantity of data entry.
Conclusion: SpA-Net enables monitoring of patients with SpA and real-life data collection, and could help improve knowledge and optimise communication between patients and care providers. Both considered SpA-Net a valuable addition to current care. Trial registration number: NTR6740.

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Impact factor: 0; nvt

Totale impact factor: 39.446

Gemiddelde impact factor: 2.320

Aantal artikelen 1e, 2e of laatste auteur: 14
Totale impact factor: 35.107
Gemiddelde impact factor: 2.508

Thoraxchirurgie

1. Technical Feasibility and Design of a Shape Memory Alloy Support Device to Increase Ejection Fraction in Patients with Heart Failure
Aarnink KM, Halfwerk FR, Said SAM, Grandjean JG, Paulusse JMJ

Purpose: Heart failure is increasingly prevalent in the elderly. Treatment of patients with heart failure aims at improving their clinical condition, quality of life, prevent hospital (re)admissions and reduce mortality. Unfortunately, only a select group of heart failure patients with reduced ejection fraction are eligible for Cardiac Resynchronization Therapy where 30-40% remain non-responders and need left ventricular support. The aim of this study is to investigate if a shape memory alloy (SMA) is able to increase the ejection fraction of a mono-chamber static heart model by 5%.
Methods: A pediatric ventilation balloon was used as a heart model (mono-chamber). Flexinol((R)), a SMA, was placed around the heart model in multiple configurations and activated using pulse width modulation techniques to determine influence of diameter and configuration on volume displacement. Furthermore, pressure within the heart model was measured with a custom-made pressure sensor.
Results: SMA with a diameter of 0.38 mm, placed in a spiral shape and activated with a duty cycle of 80% and a frequency of 50/min gave the highest ejection fraction increase of 3.5%.
Conclusions: This study demonstrated the feasibility of volume displacement in a static heart model by activation of SMA-wires. Configuration, duty cycle, frequency, pulse intervals and diameter were identified as important factors affecting the activation of SMA-wires on volume displacement. Future research should include the use of parallel SMA-wires, prototype testing in dynamic or ex vivo bench models.

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Impact factor: 1.776; Q3

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2. Randomized Trial of Miniaturized Versus Standard Extracorporeal Circulation in Aortic Valve Surgery
Halfwerk FR, Knol K, Mariani S, Grandjean JG, Mecozzi G

Background: Complications related to extracorporeal circulation remain serious. Although a minimal invasive extra corporeal circulation (MiECC) system was developed to cope with these complications, its effectivity on patient-related outcomes such as blood loss remain uncertain. Therefore, the aim of this study is to compare MiECC to an advanced standard system with respect to blood loss.
Methods: A total of 128 adult patients undergoing elective isolated aortic valve replacement were enrolled in a randomized clinical trial. Patients who had undergone previous heart surgery and with preexisting kidney failure were excluded. The primary end point was postoperative blood loss after 12 hours and at drain removal. Secondary end points included intensive care and total length of stay and intubation time. At 1 hour and 12 hours after surgery, clinical laboratory data were determined. Early clinical outcomes and long-term survival were determined.

Results: MiECC patients (n = 63) had a significant lower blood loss (230 mL, 95% confidence interval: 203 to 261 mL) than regular patients (n = 62) after 12 hours (288 mL, 95% confidence interval: 241 to 344 mL, p = 0.04). A preservation of hemoglobin levels 1 hour and 12 hours after surgery in the MiECC group were observed (p < 0.001). No difference was found in early clinical outcomes and long-term survival.
Conclusions: This randomized controlled trial compares MiECC and an advanced system for aortic valve replacement with blood loss as primary end point. We conclude that using MiECC is clinically equal for short- and long-term follow-up regarding blood loss. CLINICAL
Trial Registration: NTR3378.

Gepubliceerd: Ann Thorac Surg 2019 Jul;108(1):37-44
Impact factor: 3.919; Q1

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3. Shorter cryoballoon applications times do effect efficacy but result in less phrenic nerve injury: Results of the randomized 123 study
Molenaar MMD, Timmermans CC, Hesselink T, Scholten MF, Ter Bekke RMA, Luermans JGLM, Brusse-Keizer M, Kraaier K, Ten Haken B, Grandjean JG, Vernooy K, van Opstal JM

Background: The second-generation cryoballoon significantly improves outcome of pulmonary vein isolation (PVI) but may cause more complications than the first generation. Currently, no consensus regarding optimal cryoballoon application time exists. The 123-study aimed to assess the minimal cryoballoon application duration necessary to achieve PVI (primary endpoint) and the effect of application duration on prevention of phrenic nerve injury (PNI).
Methods: Patients <75 years of age with paroxysmal atrial fibrillation, normal PV anatomy, and left atrial size <40 cc/m(2) or <50 mm were randomized to two applications of different duration: "short," "medium," or "long." A total of 222 patients were enrolled, 74 per group.
Results: Duration per application was 105 (101-108), 164 (160-168), and 224 (219-226) s and isolation was achieved in 79, 89, and 90% (P < 0.001) of the PVs after two applications in groups short, medium, and long, respectively. Only for the left PVs, the success rate of the short group was significantly less compared to the medium- and long-duration groups (P < 0.001). PNI during the procedure occurred in 19 PVs (6.5%) in the medium and in 20 PVs (6.8%) in the long duration groups compared to only five PVs (1.7%) in the short duration group (P < 0.001).
Conclusions: Short cryoballoon ablation application times, less than 2 min, did affect the success for the left PVs but not for the right PVs and resulted in less PNI. A PV tailored approach with shorter application times for the right PVs might be advocated.

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Impact factor: 1.340; Q4

Totale impact factor: 7.035
Gemiddelde impact factor: 2.345

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

Totale impact factor: 5.695
Gemiddelde impact factor: 2.848