Wetenschappelijk onderzoek in Medisch Spectrum Twente

2020

Inhoudsopgave

Voorwoord

Voor u ligt de 12e editie van het jaarlijkse overzicht van de wetenschappelijke output van medewerkers van Medisch Spectrum Twente. Het betreft het jaar 2020. 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 2020 zijn. De zogenaamde “Epub Ahead of Print” artikelen komen in de volgende uitgave. Daarnaast worden ook peer-reviewed artikelen uit Nederlandstalige tijdschriften opgenomen.

In 2020 zijn 239 unieke publicaties verschenen in peer-reviewed tijdschriften. Dit is vergelijkbare met voorgaande jaren. De gemiddelde impact score van alle artikelen is 5.79. Dit jaar hebben we 2 keer in het absolute toptijdschrift New England Journal of Medicine gestaan, 2 keer in de Lancet en 1 keer in een subtijdschrift van de Lancet. Daarnaast stonden we nog 6 keer in een tijdschrift met een impact factor van boven de 20: Circulation, JAMA Oncology en JACC.

Daarnaast wordt per publicatie ook weergegeven in welk kwartiel het tijdschrift staat in de betreffende categorie. Indien meerdere categorieën van toepassing zijn wordt het hoogste kwartiel genomen. We publiceerden in 53% in Q1, 28% in Q2, 15% in Q3 en 4% in Q4. Dat is nagenoeg identiek aan vorig jaar.
Qua promoties was 2020 een prima jaar met 8 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 2020 naast die van eerdere jaren weergegeven.

Ik wens u veel leesplezier toe,

Prof. dr. Job van der Palen
Coördinator Wetenschappelijk Onderzoek
Medical School Twente
Medisch Spectrum Twente
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Overzicht publicaties en de Top 3

	2012	2013	2014	2015	2016	2017	2018	2019	2020
Unieke publicaties	213	191	212	245	226	216	240	232	239
Impact factor	3,97	4,38	4,03	5,06	4,70	4,47	5,64	6,12	5,79

2017			2018			2019			2020		
Top 3: Aantal publicaties:											
1	Cardiologie	31	1	Cardiologie	40	1	Heelkunde	39	1	Cardiologie	40
2	Heelkunde	30	2	Neurologie	30	2	Neurologie	33	2	Med. School	29
3	Neurologie	28	3	Longziekten	28	3	Cardiologie	27	3	Neurocentrum	29
Top 3: Totale impact factor score:											
1	Cardiologie	251	1	Cardiologie	181	1	Cardiologie	306	1	Cardiologie	433
2	Neurologie	170	2	Neurologie	136	2	Intensive care	197	2	Interne gnkd	169
3	Med. School	135	3	Heelkunde	116	3	Longziekten	148	3	MDL	145
Top 3: Gemiddelde impact factor score:											
1	Gynaecologie	16.7	1	Klin. Chemie	6.9	1	MDL	16.6	1	Oogheelkunde	17,7
2	Radiotherapie	8.2	2	Radiotherapie	6.7	2	Intensive care	14.2	2	Radiotherapie	11,4
3	Klin. chemie	6.9	3	Interne gnkd	6.1	3	Cardiologie	7.7	3	Cardiologie	10,8
Top 3: Aantal publicaties als 1e, 2e of laatste auteur:											
1	Cardiologie	18	1	Cardiologie	14	1	Cardiologie	20	1	Neurocentrum	15
2	Med. School	16	1	Longziekten	14	2	Longziekten	17	2	Cardiologie	14
3	Neurologie	14	3	Heelkunde	11	3	Neurologie	13	3	Med. School	10
						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	Interne gnkd	63
2	Longziekten	57	2	Neurologie	39	2	Longziekten	99	2	Neurocentrum	61
3	Neurologie	47	3	Longziekten	37	3	Med. School	44	3	Cardiologie	48
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	Oogheelkunde	17,7
2	Longziekten	5.1	2	Cardiologie	4.6	2	Longziekten	5.8	2	Interne gnkd	11
3	Microbiologie	4.4	3	Neurologie	3.9	3	Microbiologie	5.2	3	Intensive care	9,3

Overzicht aantal publicaties per vakgroep:

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Anesthesiologie	1	1	0	0	2	0	1	0	1	4
Cardiologie	23	33	21	25	28	39	31	40	27	40
Dermatologie	0	0	0	0	0	0	0	0	1	0
Gynaecologie	7	5	5	7	6	4	13	7	6	6
Heelkunde	26	24	13	21	31	26	30	20	39	23
Intensive Care	12	16	11	13	14	13	20	15	12	11
Interne Geneeskunde	17	15	16	20	17	8	11	24	14	27
Kindergeneeskunde	7	6	5	3	11	6	6	8	3	11
Klinische Chemie	10	6	2	6	7	5	5	7	4	8
Klinische Farmacie	4	4	4	6	8	10	3	8	13	7
Klinische Fysica	0	0	0	0	2	0	2	1	0	0
Klinische Psychologie	1	4	3	4	1	0	1	2	1	0
KNO	1	0	0	1	1	1	0	0	0	0
Longziekten	17	10	11	12	16	19	24	28	14	17
MDL	4	13	6	11	5	9	10	5	14	14
Medical School Twente	13	27	24	33	35	33	26	24	24	29
Medische Microbiologie	8	5	7	2	2	4	3	1	2	0
Mond- kaak-, aangez.chirurgie	0	1	3	0	0	1	0	1	0	0
Neurocentrum	-	-	-	-	-	-	-	-	-	29
Neurochirurgie	0	2	1	5	9	5	5	4	3	-
Neurologie	21	19	34	39	33	41	28	30	33	-
Nucleaire Geneeskunde	0	1	0	0	2	0	0	0	0	0
Oogheelkunde	0	0	0	0	0	0	0	1	0	1
Orthopedie	3	3	0	4	7	5	4	2	5	3
Pathologie	9	12	1	5	8	4	9	3	4	0
Plastische Chirurgie	1	0	2	0	2	4	4	13	12	11
Psychiatrie	0	0	0	0	1	0	4	0	0	1
Raad van Bestuur	0	0	0	0	0	0	0	0	9	10
Radiologie	6	7	6	11	14	10	4	11	2	4
Radiotherapie	5	10	3	5	12	10	4	5	4	5
Reumatologie	25	21	32	20	23	15	7	15	17	11
Revalidatiegeneeskunde	4	11	7	8	6	0	0	1	0	0
Thoraxchirurgie	5	3	4	3	2	4	5	4	3	8
Urologie	0	0	0	0	0	0	0	1	0	0

Promoties in MST in 2020

Cardiologie

Thin-strut drug-eluting stents in patients with challenging coronary lesions

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 the 19th of June 2020 at 16.45 hours

by

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Samenvatting
Sinds de introductie van medicijn-afgevende stents in de klinische praktijk in 2002, zijn deze stents onmisbaar geworden in de behandeling van patiënten met obstructief coronairlijden. De klinische uitkomsten van patiënten die een percutane coronaire interventie met implantatie van medicijn-afgevende stents ondergingen is door veel studies onderzocht. Het aantal gevallen van ongewenste klinische uitkomsten van patiënten die deelnemen aan studies is drastisch verminderd. Het gebruik van nieuwe medicatie en ontwikkelingen op stent-niveau hebben hieraan bijgedragen.

De voortdurende innovatie in coronaire stent technologie heeft geresulteerd in zeer flexibele medicijn-afgevende stents met zeer dunne stent platforms ('struts') en een biologisch afbreekbare polymeer-laag. Grootschalige klinische studies met hedendaagse stents toonden excellente uitkomsten met betrekking tot veiligheid en effectiviteit in een patiëntenpopulatie die de dagelijkse klinische praktijk weerspiegelt. Deze studies hanteren weinig selectiecriteria en worden 'all-comer' trials genoemd. Er is echter weinig data beschikbaar over de uitkomsten van patiënten met een zogenaamde 'uitdagende' anatomie van de vernauwde coronairen.

Dit proefschrift onderzocht de impact van verschillende typen medicijn-afgevende stents op de klinische uitkomsten van patiënten die deelnamen aan grootschalige gerandomiseerde all-comer trials. Het proefschrift richt zich in het bijzonder op patiënten met een uitdagende anatomie van de vernauwde coronairen.

Hoofdstuk 1 beschreef een algemene introductie met achtergrondinformatie over coronairlijden en de ontwikkelingen die plaats hebben gevonden op het gebied van medicijn-afgevende stents. De klinische potentie van hedendaagse medicijn-afgevende stents in patiënten met een uitdagende anatomie, zoals kleine vaten, bifurcatie laesies, ernstig verkalkte laesies, en laesies in het proximale segment van de 'ramus ascendens anterior' coronairarterie, werden besproken.

Hoofdstuk 2 presenteerde het primaire klinische eindpunt van de internationale, gerandomiseerde BIONYX (TWENTE IV) trial. De 2.488 'all-comers' werden gerandomiseerd naar behandeling met een nieuw soort medicijn-afgevende stent bestaande uit samengesteld metaal met een permanente polymeer-laag (de Resolute Onyx stent), of met medicijn-afgevende stents bestaande uit een zeer dunne kobalt-chroom legering met een biologisch afbreekbare polymeer-laag (de Orsiro stent). De Resolute Onyx stent was non-inferieur ten opzichte van de Orsiro stent aangaande het primaire eindpunt 'target vessel failure' (4.5% vs. 4.7%). Patiënten die behandeld waren met de Resolute Onyx stent hadden een opvallend laag aantal gevallen van stent trombose (0.1%), in vergelijking met de patiënten die behandeld waren met de Orsiro stent (0.7%).

Hoofdstuk 3 onderzocht de klinische uitkomsten van de BIONYX deelnemers na twee jaar follow-up, van wie de meerderheid geen duale antiplaatjesremming meer gebruikte tijdens het tweede jaar. Follow-up data was beschikbaar in 98.9% van alle patiënten. De studie toonde een lage en vergelijkbare incidentie van 'target vessel failure' met de Resolute Onyx in vergelijking met de Orsiro stent (7.6% vs. 7.1%). Stent trombose kwam erg weinig voor en de verschillen waren onderling niet statistisch significant verschillend (0.4% vs. 1.1%), wat tot twee jaar follow-up een vergelijkbare veiligheid van de nieuwe Resolute Onyx stent ten opzichte van de

Orsiro stent aantoonde. In een vooraf gespecificeerde subgroep analyse van patiënten die gedotterd werden in kleine coronairen (diameter < 2.5 mm), werd eveneens geen voordeel gevonden voor één van beide stents ten opzichte van de ander (target lesion failure: 6.4% vs. 6.9%).

Hoofdstuk 4 rapporteerde de 3-jaars klinische uitkomsten van 3.514 'all-comers' die deelnamen aan de gerandomiseerde, multicenter BIO-RESORT trial. Patiënten werden gerandomiseerd naar een medicijn-afgevende stent van zeer dun metaal met een biologisch afbreekbare polymeer-laag (de Orsiro stent of de Synergy stent), of een medicijn-afgevende stent met een permanente polymeer-laag (de Resolute Integrity stent). Drie jaar na stent- implantatie was de incidentie van 'target vessel failure' en andere uitkomsten laag in alle drie de stentgroepen, en werd er geen significant verschil tussen de stents gevonden.

Hoofdstuk 5 evalueerde de hypothese dat medicijn-afgevende stents gemaakt van zeer dun metaal de klinische uitkomsten van patiënten die gedotterd moeten worden in coronairen met een kleine diameter zou kunnen verbeteren. De drie medicijn-afgevende stents van de BIO-RESORT trial werden onderzocht in 1.506 patiënten die gedotterd moesten worden in kleine coronairen (diameter < 2.5 mm). Drie jaar na stent-implantatie bleek dat patiënten die behandeld waren met de zeer dunne Orsiro stent (strut-dikte 60 µm) minder vaak opnieuw in hetzelfde bloedvat gedotterd moesten worden, dan patiënten die behandeld waren met de Resolute Integrity stent (strut-dikte 91 µm; 2.1% v. 5.3%); dit verschil uitte zich vooral na het eerste jaar. Daarentegen was er slechts een numeriek (dus statistisch niet significant) verschil in het voorkomen van herhaalde dotterbehandeling bij patiënten die behandeld waren met de iets minder dunne Synergy stent (strut-dikte 74 µm), in vergelijking met patiënten die behandeld waren met de Resolute Integrity stent (4.0% vs. 5.3%). Deze resultaten ondersteunen de hypothese dat de dunste stents het meest voordelig lijken in patiënten die gedotterd moeten worden in coronairen met een kleine diameter.

In **Hoofdstuk 6** werd het belang van stent strut-dikte in coronairen met een kleine diameter bediscussieerd, in reactie op een 'letter to the editor'. We concludeerden dat de studieresultaten besproken in Hoofdstuk 5 overeenkwamen met het pathofysiologische concept dat dunnere stents mogelijk het meest relevant zijn in laesies met een kleine diameter.

Hoofdstuk 7 presenteerde de klinische uitkomsten na drie jaar follow-up van de drie BIO-RESORT medicijn-afgevende stents in 1.236 patiënten met bifurcatie laesies. De hypothese dat implantatie van de stents met zeer dunne struts (de Synergy stent en de Orsiro stent) tot een lagere incidentie van ongewenste klinische uitkomsten zou leiden (vanwege verminderde stent- overlapping van zijtakken) werd getest. De bevindingen van deze vooraf gespecificeerde sub-studie ondersteunden de hypothese niet; de incidentie van 'target vessel failure' en andere uitkomsten zoals peri-procedureel myocardinfarct, waren laag en verschilden onderling niet tussen de stents. De bevindingen werden bevestigd in een secundaire analyse in patiënten die behandeld werden met één enkele stent. Ondanks de verschillen in stent strut-dikte, soort medicijn, polymeer-type en biologische afbreekbaarheid van de polymeer-laag van de drie typen medicijn-afgevende stents, heeft dit niet geleid tot verschillen in klinische uitkomsten tot drie jaar na stent- implantatie.

Hoofdstuk 8 beschreef de klinische uitkomsten van 783 patiënten met ernstig verkalkte laesies die werden behandeld met de zeer dunne Synergy en Orsiro stents, of de dunne Resolute Integrity stent in de BIO-RESORT trial. Twee jaar na stent-implantatie bleek dat herhaalde dotterbehandelingen in hetzelfde vat minder vaak voorkwamen met Synergy (2.4%) en Orsiro (3.4%), dan met Resolute Integrity (7.7%). De studie toonde een onafhankelijke associatie tussen het gebruik van de Synergy stent en het lagere risico op herhaalde dotterbehandelingen na twee jaar. Daarentegen bestond er geen onafhankelijke associaties tussen implantatie van de Orsiro stent en een lager risico op herhaalde dotterbehandeling.

Hoofdstuk 9 toonde dat dotterbehandeling van het proximale segment van de ramus descendens anterior coronairarterie een licht verhoogd peri-procedureel risico had ten opzichte van dotterbehandeling met medicijn- afgevende stents in andere coronaire segmenten. Een aanvullende analyse toonde aan dat er, na correctie van factoren die op baseline verschilden tussen beide groepen, geen onafhankelijke associatie bestond tussen het dotteren van het proximale segment van de ramus descendens anterior en klinische uitkomsten na twee jaar follow-up. Deze data werd verkregen door een analyse van op patiënt-niveau gepoolde data van drie opéénvolgende gerandomiseerde TWENTE-trials en betrof 6.037 patiënten.

In **Hoofdstuk 10** bespraken we hoe superioriteit van de Orsiro stent werd bereikt in een gerandomiseerde multicenter trial van een andere onderzoeksgroep, waarin een complex Bayesiaans model werd gebruikt om het primaire eindpunt ‘target lesion failure’ te onderzoeken. Ons commentaar was gericht op het manuscript dat de uitkomsten van de gerandomiseerde BIOSTEMI trial in 1.300 patiënten met ST-segment elevatie myocardinfarct na één jaar follow-up rapporteerde.

Hoofdstuk 11 gaf een algemene discussie van de bevindingen in dit proefschrift en bevatte tevens aanbevelingen voor onderzoek in de toekomst.

Conclusies
Nadat medicijn-afgevende stents in de klinische praktijk werden geïntroduceerd, zijn deze effectieve stents de hoeksteen van de percutane behandeling van patiënten met obstructief coronairlijden geworden. Gedurende tientallen jaren zijn de stent ontwerpen verfijnd wat heeft geresulteerd in steeds lagere percentages van ongewenste klinische uitkomsten na percutane coronaire interventie. De twee grootschalige, gerandomiseerde BIO-RESORT en BIONYX trials hebben de lage incidentie van ongewenste klinische uitkomsten na implantatie van dunne medicijn-afgevende stents met permanente of biologisch afbreekbare polymeer-laag bevestigd in grote ‘all-comer’ patiënten populaties die de dagelijkse klinische praktijk weergeven.

De internationale, gerandomiseerde BIONYX trial in all-comers toonde uitstekende klinische uitkomsten met de nieuwe Resolute Onyx stent, in vergelijking met de Orsiro stent, na één en twee jaar follow-up. Opvallend was het zeer lage aantal gevallen van stent trombose met de Resolute Onyx stent, en deze stent toonde veelbelovende resultaten in patiënten die gedotterd moesten worden in coronairen met een kleine diameter. De gerandomiseerde, multicenter BIO-RESORT trial toonde na drie jaar follow-up lage incidenties van ongewenste klinische uitkomsten met alle drie typen medicijn-afgevende stents (Synergy, Orsiro, Resolute Integrity).

Door de lage aantallen van ongewenste klinische uitkomsten wordt het steeds moeilijker om een verschil aan te tonen in veiligheid en effectiviteit tussen verschillende medicijn-afgevende stents in grote patiëntgroepen. Het is daarom van aanzienlijk belang om deze medicijn-afgevende stents te onderzoeken in patiënten met een 'uitdagende' coronaire anatomie. Onderscheidende stentkarakteristieken zoals stent strut-dikte of radiografische zichtbaarheid zouden van bijzonder belang kunnen zijn in deze geselecteerde patiëntengroep. In subgroep analyses van de gerandomiseerde BIO-RESORT trial werden drie soorten laesies met een uitdagende anatomie onderzocht; coronairen met een kleine diameter, bifurcatie laesies en ernstig verkalkte laesies. Voor patiënten die gedotterd moesten worden in kleine coronairen, toonde de Orsiro stent veelbelovende resultaten met een opvallend laag aantal gevallen van revascularisatie. In bifurcatie laesies toonde 3-jaar follow-up dat de incidentie van ongewenst klinische uitkomsten laag was met de drie typen medicijn-afgevende stents in BIO-RESORT. De radiografische zichtbaarheid in combinatie met de zeer dunne stent strut-dikte in de Synergy stent leek voordelig in patiënten met ernstig verkalkte laesies.

Als een laesie zich in het proximale segment van de ramus descendens anterior coronairarterie bevindt dan wordt dit historisch gezien als een hoog- risico kenmerk voor percutane interventie. Ondanks dat deze coronair in het algemeen een groot deel van het myocard voorziet, toonde onze studie aan dat patiënten die in de proximale ramus descendens anterior werden behandeld niet een hoger percentage van ongewenste klinische uitkomsten hadden dan patiënten die in andere coronaire segmenten werden gedotterd.

Gerandomiseerde klinische stent studies beoordelen vaak een samengesteld klinisch eindpunt als primaire uitkomstmaat. Het gebruik van een Bayesiaans model kan het aantal patiënten dat nodig is om statistische verschillen aan te tonen reduceren, waarmee het ook de kosten van een studie verlaagt. De klinische implicaties kunnen echter onzeker zijn als een studie superioriteit van een bepaalde stent vindt aangaande het samengestelde primaire eindpunt, terwijl de opgenomen historische data en de gerandomiseerde klinische data voordelen tonen in verschillende individuele componenten van dat samengestelde primaire eindpunt.

Concluderend toonde dit proefschrift bemoedigende resultaten van dunne medicijn-afgevende coronaire stents in all-comer patiënten en in patiënten met bijzonder uitdagende anatomie van coronaire laesies. Toekomstig wetenschappelijk onderzoek moet zich focussen op lange-termijn uitkomsten, en men moet overwegen of het perspectief van de patiënt in het onderzoeken van percutane coronaire interventie en de klinische beoordeling van nieuwe medicijn-afgevende stents niet een prominentere rol moet krijgen.

Heelkunde

Overview of one decade developments of an EVAR endograft

PhD thesis

to obtain the degree of PhD at the University of Groningen
on the authority of the
Rector Magnificus Prof. C. Wijmenga
and in accordance with
the decision by the College of Deans.
This thesis will be defended in public on
Monday 19 October 2020 at 14.30 hours

by

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Supervisors: Prof. dr. J.A.M. Zeebregts
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Nederlandse samenvatting en toekomstig perspectief
Dit proefschrift gaat inhoudelijk in op drie verschillende aspecten van het abdominaal aorta aneurysma (AAA). In het eerste deel, **hoofdstuk 2** wordt de pathofysiologie en ontstaanswijze ontrafeld waarbij de verschillende factoren die van belang kunnen zijn voor AAA worden beschreven. Deze factoren zijn van belang om verdere groei van het aneurysma met verschillende interventies te kunnen bestrijden, zodat een voor de patiënt op maat gemaakte behandeling besproken kan worden. Sommige oorzaken van de AAA-groei kunnen met een computertomografie (CT)-scan in beeld gebracht worden.

Ook voor de endovasculaire behandeling ofwel in het Engels “endovascular aneurysm repair” afgekort EVAR is een CT-scan noodzakelijk om te kijken of de EVAR technische mogelijk is en om de te gebruiken endoprothese te configureren. Het is bekend dat verschillende specialisten bij beoordeling van de CT-scan gegevens van een patiënt ook tot verschillende afwegingen kunnen komen om een EVAR- behandeling te doen. De planning van en de keuze voor een bepaalde prothese kan hierbij dus variëren tussen specialisten en hiermee dus ook de eventuele uitkomst van behandeling. Dit wordt besproken in **hoofdstuk 3** van dit proefschrift.

Het derde deel (**hoofdstuk 4-7**) gaat inhoudelijk over één type endoprothese, te weten de Anaconda™ AAA Stent Graft System. Gedurende de afgelopen jaren zijn er drie generaties/opeenvolgende types van deze endoprothese op de markt gekomen. We bestuderen hierbij de resultaten van de tweede en derde generatie endoprothese bij gebruik in “normale” AAA-anatomie en meer uitdagende AAA-anatomie. We proberen hierbij oorzaken te vinden waarom sommige gebruikte endoprothese in de verschillende generaties bij sommige patiënten toch geen goed resultaat geven bij de behandeling. Mede door deze resultaten zijn ook aanpassingen aan de prothese doorgevoerd in de derde generatie die wat betreft uitkomsten van behandeling in de derde generatie weer vergeleken worden met de tweede generatie endoprothese.

Het exacte mechanisme van AAA-groei is niet bekend, maar multifactoriële invloeden evenals biomechanische aspecten spelen een rol, waarbij deze laatste factor ook van belang is voor het ontwerp van de endoprothese. Aneurysma specifieke eigenschappen zoals trombus, verkalking, maar ook andere wand gerelateerde factoren beïnvloeden de afdichting en houvast van de endoprothese in de aorta. Als onderdeel van een hoofdstuk uit een boek betreffende AAA en EVAR geven we in **hoofdstuk 2** relatief beknopte samenvatting en overzicht van factoren die de groei en ruptuur kans van een aneurysma beïnvloeden. Basaal onderzoek over pathofysiologische processen in het wandstandige AAA-trombus wordt beschreven. Effecten van andere bekende risicofactoren uit screening en cohortstudies zoals diabetes mellitus en roken worden beschreven. Roken is hierbij waarschijnlijk de belangrijkste te vermijden risicofactor voor het ontstaan van AAA en zijn verdere groei. Uitleg wordt gegeven omtrent het samenstel tussen de wandstandige (intraluminale) trombus (ILT) en de aortawand als oorzaak van verzwakking van de aanvankelijk sterke aortawand. Hoe deze ILT eventueel beïnvloed kan worden om de aortawand minder te laten verzwakken wordt eveneens besproken. Invloed van deze ILT, maar ook andere factoren zoals oxidatieve stress, neovascularisatie en aanwezige immuunrespons bepalen allemaal de sterkte van de onderdelen van de aortawand, samengevat in de extracellulaire matrix (ECM). Deze ECM-sterkte

bepaalt mede de weerstand en souplesse van aortawand tegen de continue bloeddrukveranderingen veroorzaakt door de bloedstroom. De mogelijkheid om deze AAA-groei en ruptuurkans eventueel te verminderen met medicijnen wordt ten slotte in dit hoofdstuk ook nog beschreven.

Als de mogelijkheid voor een EVAR beoordeeld wordt, bepalen anatomische patiënt specifieke factoren het keuzeproces van de te gebruiken type endoprothese. De tweede generatie Anaconda™ AAA-endoprothese werd in 2003 als een van de nieuwe endoprothese geïntroduceerd. Bij gebruik van een nieuw type endoprothese moet de vaatchirurg ervaring krijgen in het bepalen van de optimale maten van de prothese bij een specifieke patiënt, hierbij wordt de chirurg ook ondersteund door de fabrikant. Het opbouwen van deze ervaring, met name voor junior vaatchirurgen kan in principe ook versneld worden via e-learning modules. Wij testen en valideren een leeromgeving waarbij de anatomische AAA-maat gegevens van verschillende patiënten gepresenteerd worden. In deze leeromgeving kunnen drie verschillende merken endoprotheses gekozen worden die in die tijd ook daadwerkelijk gebruikt werden in de dagelijkse praktijk.

In deze studie, beschreven in **hoofdstuk 3**, analyseert een groep van 5 ervaren EVAR-vaatchirurgen de anatomische gegevens van 202 patiënten met een AAA en beoordeeld hierbij de mate van geschiktheid van elk van de drie types endoprothese die hij kan gebruiken.

In totaal worden er 3030 beoordelingen gedaan waarbij een gekwantificeerde uitspraak wordt gedaan omtrent de ingeschatte kans op een succesvolle afdichting en fixatie van de endoprothese in de AAA. De Delphi-methode wordt hierbij als statistiek gebruikt om de mate van overeenstemming in besluitvorming tussen vaatchirurgen te beoordelen. De kappa analyse wordt gebruikt om de variatie in deze besluitvorming tussen de gegeven antwoorden te bepalen. Als cohort patiënten bekeken is de mate van overeenstemming van de gekwantificeerde uitspraak tussen ervaren vaatchirurgen behoorlijk groot met een Cronbach waarde tussen 0.87 en 0.90. Bekeken op individueel niveau van patiënt beoordeling kon er een behoorlijke variatie in de gekwantificeerde uitspraak zijn tussen de vijf vaatchirurgen. Dit hoofdstuk kijkt naar de variatie in dit keuzeproces tussen verschillende ervaren EVAR-vaatchirurgen. We schatten in dat goed ontwikkelde algoritmes in een beslissing ondersteunende omgeving de keuze van een specifieke endoprothese bij EVAR bij een specifieke patiënt mede kunnen helpen te bepalen en dat dit systeem dan ook internationaal als standaard ondersteuning te gebruiken zou zijn. Met deze gevalideerde en met continue verbeteringen aangepaste algoritmes voor protheses kan de patiënt beschermd worden tegen onopgemerkte fouten in de interpretatie van gegevens, kunnen eventuele leercurves versneld worden en kunnen nieuwe versies van endoprotheses met internationaal input van experts in de algoritmes bij gebruik in de dagelijkse praktijk eerder mede beoordeeld worden op geschiktheid.

De introductie van een nieuwe endoprothese gaat in het algemeen samen met een patiënt gecontroleerde prospectieve studie om de klinische resultaten te monitoren bij gebruik van de endoprothese volgens de toegestane gebruiksvoorschriften - “instructions for use” (IFU) - van de fabrikant. Het is belangrijk bij gebruik van de nieuwe endoprothese dat de technische en klinische studieresultaten gelijk of gunstiger zijn in vergelijking met de tot dan toe gebruikte endoprotheses, anders is

het niet te verwachten dat vaatcentra die niet met de studie meedoen de endoprothese ooit gaan gebruiken

In **hoofdstuk 4** van dit proefschrift beschrijven we de resultaten van de tweede generatie Anaconda™ AAA endograft binnen de gebruiksvoorschriften. De tweede generatie endoprothese heeft proximale haakjes die verbonden zijn met de proximale dubbele ringstents zonder ondersteuning van ringstents in de endoprothese body. Het idee van de haakjes was het verminderen van de mogelijkheid van verzakken van de endoprothese vanuit de “hals” in het aneurysma zelf, maar ook de kans van zogenaamde type-1 lekkage van bloed langs de buiten- en bovenzijde van de endoprothese tussen de aortawand en de prothese in het aneurysma van de aorta zelf. In een internationale multicenter, prospectieve, niet gerandomiseerde studie worden in totaal 61 patiënten in negen verschillende klinieken geïncludeerd. De primair technische succesvolle behandeling (30 dagen) was 96.7% en met een extra operatieve interventie tijdens de ingreep in de vorm van een proximale cuff i.v.m. een type-1 endoleak zelfs 98.4%. Er waren drie “clinical failures” (4.9%) na 30 dagen waarbij 1 conversie naar een open operatie nodig was. Na 2 jaar follow-up waren er in totaal 7 clinical failures waarbij de endoprothese niet voldeed aan de vooraf gedefinieerde eisen van succesvolle plaatsing en aanwezigheid van de prothese bij de patiënt. Er werden negen herstel behandelingen uitgevoerd waarvan twee keer voor dichtzittende pootjes van de endoprothese. Er is niemand gedurende de studie overleden aan de gevolgen van het aneurysma zelf. Ook is de endoprothese niet los gaan zitten in de hals en zijn de metalen onderdelen van de endoprothese niet gebroken tijdens de studieperiode. De omvang van het aneurysma zelf is van 57 mm naar 45 mm significant kleiner geworden in de 24 maanden van de nacontrole van patiënten.

We concluderen in deze studie dat de tweede generatie Anaconda™ endoprothese makkelijk te plaatsen is en ook effectief is in zijn werking gedurende de geanalyseerde studieperiode bij binnen bepaalde grenzen gedefinieerde AAA-anatomie.

Met de gunstige ervaringen van het gebruik van de Anaconda™ binnen de gebruiksvoorschriften van de fabrikant werd door de vaatchirurgen ook EVAR-indicaties buiten de voorgeschreven gebruiksvoorwaarden gekozen. Een van de belangrijkste exclusie-criterium bij AAA-patiënten die gescreend worden voor EVAR is een (te) sterke hoek tussen de aorta nek waar de prothese zich moet vasthouden en de daadwerkelijke AAA zelf. Met een goed ontworpen endoprothese waarbij biomechanisch de prothese zich stevig kan fixeren aan de wand van de gehoekte hals overgang naar het aneurysma kan langdurige endoleak type-1 vrije fixatie mogelijk zijn. Om dit te onderzoeken beschrijven we in hoofdstuk 5 de resultaten van een multicenter studie waarbij de Anaconda™ endoprothese in fors gehoekte infrarenale hals anatomie is geplaatst.

Uit eerdere studies was al bekend dat bij ernstige infrarenale hals hoeken van meer dan 60 graden de uitkomsten van EVAR minder gunstig zijn. Aanpassingen van endoprotheses met speciale aandacht voor flexibiliteit, proximale houvast en goede afsluiting bij de halswand kan de kans op type-1 endoleak en endoprothese migratie verminderen. Door de specifieke eigenschappen van de Anaconda™ met het prothese lijfje zonder stent ringen en het flexibele inbreng systeem van de

endoprothese kan, in theorie de Anaconda™ zeker geschikt zijn voor plaatsing in gehoekte infrarenale hals anatomie buiten de gebruiksvoorwaarden.

In deze studie participeerden in totaal 36 AAA-patiënten uit 9 Nederlandse ziekenhuizen. Een totale follow-up duur van 40 maanden werd bereikt waarbij de infrarenale hals hoek gemiddeld 82 graden was (60-133 graden). De gemiddelde aneurysma diameter was 71 mm, variërende tussen 45 mm (symptomatisch klein AAA) tot 100 mm.

De primair technische succesvolle behandeling (30 dagen) was 83% en met een extra operatieve interventie 94%. Er is niemand gedurende de studie van 4 jaar overleden aan de gevolgen van het aneurysma zelf, maar wel 8 patiënten aan andere oorzaken. De 4-jaars primair klinische succesvolle behandeling was 68% en met extra interventie direct 75% en in latere fase ook 75%. 8 van de 11 klinische failures traden op in de eerste 12 maanden. In de totale studie-periode zijn 5 endoprothese pootjes en 2 prothese lijfjes dicht gaan zitten met stolsels (occludeerden). Deze minder gunstige resultaten werden in deze studie eveneens uitgebreider besproken. Er was 1 endoprothese die uitzakte vanuit de hals zodat een type-1 endoleak kon optreden. In deze studie concluderen we dat open AAA-herstel bij AAA-anatomie met een forse hals hoek nog steeds de voorkeur heeft indien de patiënt ook lichamelijk fit genoeg is voor deze open ingreep. Het lijkt verstandig te zijn indien EVAR alsnog wordt toegepast bij uitdagende anatomie zoals een sterk gehoekte aorta hals, deze procedure mede vanwege de hogere kans op type-1 endoleak, hals verwijding en uitzakken van de prothese, in centra met ervaring in complexe anatomie uit te voeren.

Door de toename in gebruikservaring werd de EVAR wereldwijd ook gebruikt bij de (contained) geruptureerde AAA-patiënten. Met name de 30-dagen mortaliteit na EVAR bij AAA-ruptuur leek gunstiger te zijn t.o.v. de uitkomsten na open AAA-operatie.

In **hoofdstuk 6** beschrijven we de korte en lange termijn resultaten van de Anaconda™ bij EVAR bij AAA-rupturen (rEVAR). In deze studie wordt in 1 ziekenhuis prospectief, niet gerandomiseerd een totaal aantal van 117 patiënten met een AAA-ruptuur geïncludeerd in de periode 2006-2010. De patiënten werden tijdens de opvang beoordeeld middels CT-scan op anatomische geschiktheid waarbij een gecontroleerde hypotensie werd nagestreefd totdat duidelijk was op welke manier de operatie van het AAA het best mogelijk was. In totaal zijn 70 patiënten middels open uitschakeling van het AAA behandeld, 35 met EVAR waarbij 27 patiënten de Anaconda™ bifurcatie prothese geplaatst kregen en 8 patiënten de Talent™ of de Endurant™ endoprothese door ofwel niet geschikte iliacale toegang ofwel niet geschikte fixatie voor de Anaconda™ endoprothese. Ongeveer 30% van de rEVAR patiënten had eveneens een uitdagende hals anatomie met een halslengte korter dan 15 mm ofwel een hals hoek van 60 graden of meer. Na de rEVAR werd binnen 30 dagen bij 26% een re-interventie uitgevoerd. De 30-dagen, 1 jaar en 5 jaar mortaliteit na rEVAR was 17%, 26% en 42% respectievelijk. Alle overleden patiënten na 1 jaar follow-up waren niet aneurysma gerelateerd. Ook een uitdagende hals anatomie was niet extra nadelig voor de sterftecijfers.

In deze studie bespreken we dat rEVAR gebruikt kan worden als een “damaged controle” operatie principe, waarbij minder gunstige anatomie ook middels EVAR kan

worden geopereerd indien de mogelijkheid van een toename in secundaire interventie hierbij als nadelige consequentie geaccepteerd wordt. Deze conclusie is recent ook bevestigd in een systematische review waarbij rEVAR in geselecteerde patiënten een goed alternatief is in plaats van de open AAA uitschakeling[1].

Gedurende dit promotietraject bleek ook in de door ons uitgevoerde studies met de Anaconda™ endoprothese dat het aantal dichtzittende/getromboseerde Anaconda™ pootjes meer te zijn dan verwacht. Hoewel dit aantal in vergelijking met andere type endoprotheses in de literatuur niet significant hoger was, bleek het wel in de onderlinge vergelijkingen met andere (ook oudere) endoprotheses in de hoogste groep van dichtzittende pootjes te zitten. In **hoofdstuk 7** evalueren we de incidentie en behandeling van de dichtzittende poten in zowel de tweede generatie als de derde generatie Anaconda™ endoprothese. De derde generatie prothese die de Anaconda One-Lok™ wordt genoemd werd geïntroduceerd in 2011. Hierbij werd de Anaconda One-Lok™ lijfje met poot combinatie voor de verschillende te kiezen afmetingen gestandaardiseerd.

In deze retrospectieve studie wordt in 1 ziekenhuis prospectief de gegevens verzameld van in totaal 317 geïncludeerde patiënten van 2003 tot aan september 2015. De primaire uitkomst parameter was poot occlusie. In 189 patiënten werd de tweede generatie Anaconda™ endoprothese geplaatst en bij 128 patiënten de derde generatie Anaconda One-Lok™.

Bij 71% van de patiënten werd de operatie electief gepland uitgevoerd, bij 12% was er sprake van een symptomatisch AAA en bij 17% was er sprake van een AAA-ruptuur. In totaal werden 184 patiënten binnen de gebruiksvoorschriften van de Anaconda™ geopereerd. Na een gemiddelde follow-up duur van 47 maanden (range 0-134 maanden) werden initieel 27 dichtzittende pootjes en 4 dichtzittende lijfjes gediagnostiseerd. Van de tweede generatie Anaconda™ was 86.5% van de patiënten na 5 jaar occlusie vrij en 88.6% voor de derde generatie Anaconda One-Lok™ endoprothese. Dit was niet statisch significant verschillend. Poot occlusie resulteerde in dit cohort niet in kleine of grote amputaties. In totaal vijf patiënten werden open geopereerd door occlusie van het lijfje van de endoprothese. Indien 1 pootje dicht zat werd trombectomie, rekanalisatie van de poot met stenting, femoro-femorale bypass-chirurgie ofwel conservatieve behandeling verricht. Er was een verband tussen poot occlusie en kleinere distale prothese poot diameter bij zowel de tweede als de derde generatie prothese. In de tweede generatie bleek dat de timing van de operatie ook gerelateerd was aan meer poot occlusie, wat bleek uit procentueel de meeste occlusies in de symptomatische AAA-operatiegroep.

We concluderen met deze studie dat de Anaconda™ endoprothese een bewezen geschikte endoprothese is voor AAA-uitschakeling in dagelijks gebruik binnen de gebruiksvoorschriften van de fabrikant. Een substantieel aantal occlusies manifesteren zich tussen de 2 en 5 jaar follow-up zodat alertheid in diagnostiek in risicogroepen voor occlusie zinvol is. Het gebruik van intensievere follow-up programma's in deze jaren kan het aantal poot occlusies waarschijnlijk verminderen.

Toekomstig perspectief
De definitieve behandeling en/of preventie van het abdominaal aorta aneurysma behoeft als basis een diepgaande kennis van de factoren die het AAA laten ontstaan, laten groeien en verder laten verslechteren tot en met de eventuele ruptuur van het aneurysma. Ontsteking, artherosclerose met intraluminale trombusvorming en erfelijke factoren zijn de onderzoekslijnen waar primair het wetenschappelijk pathofysiologische AAA-onderzoek op gericht is. De effecten van metformine, stamcel behandeling en factoren die de extracellulaire matrix verstevigen worden verder onderzocht. De niet chirurgische behandelingen moeten met name gestart worden in de vroegere fases van AAA-ontwikkeling waarbij het aneurysma diameter nog beperkt is[2].

Bevolkingsonderzoek voor AAA-screening bij mannen van 65 jaar is klasse 1, level A-bewijs als zijnde effectief. De Europese richtlijnen raden dan ook aan een nationaal bevolkingsonderzoek te starten voor AAA screening[3]. In een Nederlands onderzoek van de Gezondheidsraad daarentegen wordt geconcludeerd dat voor de Nederlandse situatie een AAA-bevolkingsonderzoek negatieve gevolgen zou hebben in termen van risico's en opbrengsten. De opsporing van AAA in Nederland middels een bevolkingsonderzoek met de huidige goed georganiseerde huisartsenzorg en de gunstige resultaten van de Nederlandse AAA-behandeling in vergelijking met omliggende landen is niet zo gunstig meer als men aanvankelijk dacht. Hoewel er wel een risico reductie optreedt, maakt me zich ook zorgen omtrent de emotionele belasting van de screening voor de op te roepen bevolkingsgroep. Door verder optimalisatie in de eerstelijns zorg met betrekking tot preventie van en alertheid op de AAA kan het nut van de screening nog verder geminimaliseerd worden[4].

Eenvoudige in te zetten diagnostiek zoals echo-duplex onderzoek is in opkomst in de eerstelijns zorg en kan het nut van AAA-screeningsprogramma's nog meer reduceren. Het detecteren van AAA- aanwezigheid en groei kan ook onderdeel worden van een breder Nederlands gezondheid en ziekte preventieprogramma. Andere nog op te zetten bevolkingsonderzoeken zoals longkanker detectie middels thorax CT-scans bij hoogrisico groepen zoals rokers kan zelfs gecombineerd worden met eenzelfde CT-scan voor het eerste moment van AAA-screening. De totale gezondheidswinst van deze gecombineerde screening kan zelfs meer zijn dan verwacht.

Met betrekking tot de interobserver variabiliteit in het plannen en meten van de EVAR-endoprothese zijn juiste meet instrumenten met uniforme afspraken omtrent AAA-anatomie meting zinvol. Ook het gebruik van goed uitgewerkte klinische relevante selectie en "decision support" programma's kunnen onwenselijke interobserver variatie verminderen[5].

Het moet toch ook mogelijk zijn om een grote AAA-database te creëren waarbij de European Society of Vascular Surgery een EU brede database opzet waarbij alle type endografts en de anatomische AAA-data en patiënt karakteristieken in opgenomen worden. Dit zal bij voorkeur in een prospectief register gedaan moeten worden waarbij de Europese Unie samen met de nationale gezondheid organen zorgt dat de bedrijven van de endoprotheses hier een significante bijdrage in leveren om dit te financieren. De European Society of Vascular surgeons zal hierbij een ook een financiële bijdrage moeten ontvangen om het tijdrovende invullen van de database te

organiseren en (op nationaal vaatchirurgisch niveau) te financieren. De follow-up data zal dan nationaal ingebracht kunnen worden om de noodzakelijke “post-implant surveillance” Europees mogelijk te maken.

Gedurende de eerste periode van EVAR is vanaf 1996 al een vrijwillig multicenter register van start gegaan - The European Collaborators on Stent-Graft Techniques for Abdominal Aortic Aneurysm Repair (EUROSTAR) waarbij EVAR-patiënten gedurende de follow-up bijgehouden worden. In de EVAR-begintijd waren 60% van de patiënten ASA III hoog risico waarbij de inclusiecriteria minder strikt dan nu met AAA-diameters vanaf 4 centimeter. Dit succesvolle register heeft vanaf de eerste generatie tot en met de derde generatie endoprothese onderzoeksresultaten gegeneerd, waarbij de inclusie in 2006 is geëindigd. Recente onderzoeksresultaten waarbij het effect van gender op de 30-dagen en 5-jaars follow-up resultaten na EVAR beschreven worden, geeft nogmaals het belang weer van een register waar data verzameld wordt vanuit de dagelijkse klinische praktijk[6].

Hoewel gerandomiseerde clinical trials en systematische reviews wetenschappelijk de gouden standaarden zijn, is een goede lange termijn registratie waarbij verschillende type endoprotheses en updates in tijd bijgehouden worden zonder eventuele inhoudelijke beïnvloeding van de fabrikant zelf ook erg belangrijk. Wanneer de database zodanig groot is dat “big data” analyse nodig is kunnen zelfs modernere analysetechnieken als Deep Learning/Artificial Intelligence ingezet worden. Deze technieken zijn waardevol voor data-analyse waarbij patroonherkenning onderzoek gedaan kan worden in de combinatie endoprothese en patiënt gerelateerde anatomische data en klinische uitkomst. De gebruiksvoorschriften (Instructions for use) kunnen dan aangepast worden als complicaties optreden in specifieke patiëntgroepen en vroegere herkenning van potentiële endoprothese ontwerpfouten kan dan beter mogelijk zijn.

Inzicht in het gedrag van de Anaconda™ endoprothese in de tijd in relatie met de AAA-anatomie van de patiënt is het doel van de onderzoekslijn “Longitudinal Study to Pulsatility and Expansion in Aortic Stent grafts (LSPEAS-study)” [7,8]. Het interactieproces tussen de endoprothese en het AAA van de patiënt is een tijdsafhankelijk fenomeen waarbij het ultieme behandeldoel is het voorkomen van de aneurysma ruptuur zonder allerlei bijkomende complicaties of noodzakelijke heroperaties[9].

De volgende stap in de voorspelling van het gedrag van de endoprothese in individuele patiënten in de tijd is gebruik te maken van ECG-getriggerde dynamische CT-scanning waarbij de endoprothese en de aorta wand gedurende de beweging geobserveerd kan worden. Gedurende de follow-up periode heeft de continue cyclus van hartslag en aorta bloeddoorstroming invloed op de afdichting en fixatie van de endoprothese tegen de aortawand waarbij kennis van optredende veranderingen hierin gebruikt kan worden om complicaties en eventuele clinical failures van de prothese in de nabije toekomst te voorspellen.

Recente 3D CT-onderzoek omtrent het uitzetten en remodelleren van de proximale deel van de Anaconda™ in de aorta hals geeft een uniek inzicht in de mechanische eigenschappen in de tijd van de zadelvormige proximale deel van de Anaconda™ endoprothese. Hoewel in het begin “oversizing” (kiezen van een grotere maat

prothese t.o.v. de aorta hals diameter) belangrijk is om goede grip en afdichting te krijgen, zie je ook dat de definitieve endoprothese ring diameter zich zodanig gaat hervormen in de aorta dat de normale diameter van de endoprothese van voor het inbrengen weer binnen 6 maanden zo'n beetje bereikt wordt. De aorta wand tpv aortahals van de patiënt past zich hierbij dan ook aan de uitgangsvorm van de endoprothese aan[10,11]. Vervolgen van dit fenomeen met behulp van ECG-getriggerde dynamische CT-onderzoek kan mogelijk in de toekomst hals anatomie eigenschappen voorspellen die vatbaar zijn voor Type-1A endoleak of endoprothese gerelateerde hals aneurysma's.

Intensievere op maat gemaakte follow-up schema's kunnen dan gemaakt worden voor patiënten die vatbaar zijn voor de mogelijke complicaties en minder stringente schema's zijn dan mogelijk voor de "recht toe recht aan" patiëntencategorie. De toename in röntgenstralen belasting bij intensiever follow-up schema's bij geselecteerde patiënten blijft daarbij wel binnen de limieten gezien de leeftijd van patiënten en de continue verbeteringen in CT-apparatuur. De infrarenale hals vorm met mogelijke hoeken vanaf 0 tot wel 90 graden of meer een belangrijk selectiecriterium voor open ofwel EVAR-behandeling van het AAA.

Ook het voorspellen van complicaties van de endoprothese in de distale landingszone in de bekkenslagaders is onder invloed van de werking van tijd. We zagen dat het dichtzitten van de endoprothese poot door trombus vorming relatief hoog was in 1 van onze Anaconda™ studies. In de tijd lijkt de uitbochting van de poot van de endoprothese met name aan de rechter iliacale zijde toe te nemen, de zijde die ook gebruikt wordt voor het inbrengen van de endoprothese. De flexibele Anaconda™ poot ontwerp heeft de vorm van een stofzuigerbuis maar het nadeel van de hoge flexibiliteit is het optreden van het zogenaamde "Concertina effect" wat kan resulteren in verstoringen van het doorstromingsprofiel in de poot[12]. Aanvullend onderzoek kan mogelijk aanwijzingen geven hoe het doorstromingsprofiel van de poot verder verbetert kan worden zonder de flexibiliteit van de poot hiervoor op te geven.

Met gebruik van contrast-versterkende echo deeltjes gedurende de follow-up kan de karakteristieke real-time doorstromingsprofielen in de iliacale anatomie gecontroleerd worden met als doel eerder voorspellen en voorkomen van mogelijk aorta-iliacale poot occlusie in de aankomende follow-up periode[13].

Het combineren van de kennis en ervaring van vaatchirurgen, interventie radiologen en technisch geneeskundige gezamenlijk in een vasculair team zal de gouden standaard moeten zijn in de klinische en wetenschappelijke vaatprogramma's.

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Longgeneeskunde

Midrange-proadrenomedullin as a marker for mortality and morbidity in COPD

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 Wednesday the 24th of June 2020 at 12.45 hours

by

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Samenvatting

Chronische obstructieve longziekte (COPD) is gedefinieerd als een te voorkomen en behandelbare ziekte die wordt gekenmerkt door aanhoudende ademhalingssymptomen en beperking van de luchtstroom als gevolg van luchtweg- en/of alveolaire afwijkingen. Deze wordt meestal veroorzaakt door blootstelling aan schadelijke deeltjes of gassen, vooral tabaksrook. COPD is een heterogene en complexe ziekte en wordt gekenmerkt door acute exacerbaties van COPD (AECOPD), die de geleidelijke achteruitgang van de longfunctie kunnen versnellen en het risico op overlijden verhogen. Bovendien worden AECOPD geassocieerd met een verhoogd risico op ziekenhuisopname, een lagere levenskwaliteit en hogere kosten voor de gezondheidszorg. Het is relevant om te kunnen voorspellen welke patiënten een verhoogd risico hebben om te overlijden en een verhoogde kans op exacerbaties en opnames om zo patiënten te kunnen identificeren bij wie een wijziging in het beleid nodig kan zijn. Er is groeiende belangstelling voor biomarkers om de heterogeniteit van ziekte in kaart te brengen en progressie te voorspellen. Een mogelijke biomarker is midrange-proadrenomedullin (MR-proADM), de stabielere voorloper van adrenomedulline (ADM). ADM heeft immuunmodulerende, metabole en vasculaire eigenschappen.

Het belangrijkste doel van dit proefschrift is gewijd aan het onderzoeken of MR-proADM geassocieerd is met morbiditeit en mortaliteit bij COPD-patiënten.

In **hoofdstuk 2** werd MR-proADM gemeten in een subgroep van 181 patiënten uit de COMIC-studie (“Cohort van Mortaliteit and Inflammatie in COPD”) met een bloedmonster in stabiele fase. We toonden aan dat hoge niveaus van MR-proADM in stabiele fase geassocieerd zijn met een drievoudig verhoogd sterfterisico wanneer gecorrigeerd voor mogelijke verstorende variabelen. Het drievoudig verhoogde risico is zeer relevant, vooral omdat het absolute sterfterisico in deze studie hoog was, waarbij tot 23% een overlevingskans heeft van minder dan 2 jaar. MR-proADM zou gebruikt kunnen worden in het proces van klinische besluitvorming.

Een belangrijke stap in de ontwikkeling van biomarkers, naast de ontdekking ervan, is het valideren van deze biomarkers om er zeker van te zijn dat de test betrouwbaar, reproduceerbaar, voldoende sensitief en specifiek is voor het voorgestelde gebruik.

In **hoofdstuk 3** hebben we gereageerd op een ingezonden brief van Dr. Khorfan aan de editor van CHEST waarin hij voorstelde om de afkapwaarde te valideren bij een andere groep patiënten. We waren het eens met het belang van validatie en hebben onze vervolgstappen voor aanvullend onderzoek uitgelegd.

In **hoofdstuk 4** zijn de afkapwaarden uit hoofdstuk 2 in stabiele fase en de afkapwaarde zoals eerder bestudeerd door Stolz et al. gevalideerd in een andere subgroep van 545 patiënten uit de COMIC-studie. Deze validatiestudie bevestigde dat hoge MR-proADM-spiegels, gemeten bij patiënten met COPD in stabiele fase, geassocieerd waren met een hoger sterfterisico. We toonden een 1,9- en 2,2-voudig verhoogd risico aan, op sterfte na 2 jaar bij afkapwaarden van MR-proADM gemeten in stabiele fase, van respectievelijk 0,71 en 0,75 nmol/l. Het absolute sterfterisico in deze populatie was aanzienlijk: 13% overleefde de eerste twee jaar niet. Hieruit concludeerden we dat MR-proADM gemeten in stabiele fase een valide en klinisch relevante biomarker is.

In dit proefschrift hebben we ook procalcitonine (PCT) bestudeerd als potentiële biomarker voor het voorspellen van sterfte. PCT is een marker voor systemische bacteriële infectie, PCT is verhoogd bij ziekenhuisopname voor een AECOPD en wordt geassocieerd met slechtere prognoses van ziekenhuisopname, langere opnameduur en opname op de intensive care. In onze studie wilden we van PCT gemeten in stabiele fase het verband met sterfte bevestigen. In **hoofdstuk 2** lieten we zien dat dat PCT waarden van patiënten met een verhoogd sterfterisico niet afweken van waarden van mensen met een lager sterfterisico. Omdat onze bevindingen hetzelfde waren als de resultaten van een eerdere studie van Stolz et al., denken we dat PCT geen belangrijke biomarker is om sterfte te voorspellen bij COPD in zowel stabiele fase als bij ziekenhuisopname voor AECOPD.

Een andere goed bestudeerde biomarker bij COPD is fibrinogeen. Fibrinogeen wordt door de Amerikaanse Food and Drug Administration (FDA) en de European Medicine Agency (EMA) als voorspellende biomarker bij COPD geaccepteerd. Naast een stollingsfactor is fibrinogeen ook een acute fase-eiwit. In **hoofdstuk 5** beschreven we dat fibrinogeen, gemeten in het COMIC-cohort in stabiele fase, een voorspeller is voor overlijden bij COPD. Een verdubbeling van de fibrinogeenwaarde bleek een 2,39 (95% BI 1,41-4,05) keer verhoogd sterfterisico te geven.

Omdat COPD een complexe en heterogene ziekte is, is het onwaarschijnlijk dat één enkele biomarker het ziekteverloop kan voorspellen. In hoofdstuk vijf hebben we daarom MR-proADM gecombineerd met fibrinogeen om het voorspellen van het sterfterisico te optimaliseren. We ontdekten dat het toevoegen van MR-proADM aan fibrinogeen de nauwkeurigheid van het voorspellingsmodel voor sterfte op korte termijn (follow-up van één jaar) significant en relevant verbetert. Het gecombineerde model was echter niet beter in het voorspellen van sterfte op korte termijn in vergelijking met een model met uitsluitend MR-proADM.

Er zijn verschillende multidomeinscores voor het voorspellen van het ziekteverloop binnen COPD beschikbaar. Hoewel deze multidomeinscores uit meerdere componenten van de heterogene ziekte bestaan, wordt de systemische component van COPD niet voldoende meegenomen in deze scores. In hoofdstuk zes hebben we MR-proADM (afkapwaarde van 0,87 nmol/l) gecombineerd met de ADO (leeftijd, dyspneu and luchtweg obstructie) de vernieuwde ADO en de BOD (BMI, luchtwegobstructie en dyspneu). In een samengevoegde dataset van twee grote Europese prospectieve observationele cohortstudies (COMIC en de PROMISE-COPD-studie) hebben we MR-proADM toegevoegd aan deze multidomeinscores. Het toevoegen van MR-proADM aan de ADO, vernieuwde ADO en BOD verbeterde de sterftevoorspelling van alle drie de multidomeinscores. De toegevoegde voorspellende waarde van MR-proADM voor zowel de ADO, vernieuwde ADO en BOD-index laat zien dat het toevoegen van de systemische component meerwaarde heeft. Daarnaast bleek dat de ADOA-index en de vernieuwde ADOA-index numeriek een beter voorspellend vermogen hebben dan de BODA-index.

Het doel van de studie, zoals beschreven in hoofdstuk zeven, was om het verband tussen MR-proADM (gemeten in stabiele fase) en toekomstige ernstige AECOPD (waarvoor ziekenhuis opname nodig is) en longontsteking te bekijken. Uit de analyses in onze samengevoegde dataset van de COMIC- en de PROMISE-COPD-studie

bleek MR-proADM, gemeten in stabiele fase, een belangrijke biomarker te zijn voor voorspellen van een toekomstige ernstige AECOPD. Een hoog niveau (≥ 0,87 nmol) MR-proADM, gemeten in stabiele fase, ging gepaard met een 30% verhoogd risico op het krijgen van een ernstige AECOPD (HR 1,30 (95% BI 1,01-1,68)). Met 25% van de patiënten met een hoge MR-proADM waarde in stabiele fase en met 34% (cumulatief deel) van de patiënten met ten minste één ernstige AECOPD in de 3 jaar follow-up, zijn onze resultaten klinisch relevant. Overigens bleek, zoals ook bekend uit de literatuur, een eerdere ziekenhuisopname voor een AECOPD (1 jaar voorafgaand aan deelname aan de studie) ook sterk geassocieerd met het risico op het krijgen van een AECOPD (HR 1,90 (95% BI 1,51-2,40)).

In **hoofdstuk 8**, de algemene discussie, vatten we onze bevindingen samen en een zetten we deze in een bredere context. Dit hoofdstuk wordt afgesloten met aanbevelingen voor verder onderzoek. De belangrijkste hiervan worden hieronder samengevat.

In dit proefschrift concluderen we dat MR-proADM, gemeten in stabiele fase, een valide en klinisch relevante biomarker is. Hoewel we denken dat dit een belangrijke conclusie is, zien we dat het nog niet in de praktijk gebruikt wordt. Nu is aangetoond dat MR-proADM verband houdt met sterfte, moeten we ons concentreren op de manier waarop het voorspellen van sterfte kan leiden tot verbeterde patiëntenzorg. Om een klinische beslissing te nemen is het belangrijk om de juiste afkapwaarde van MR-proADM te kiezen. Tot nu toe werd als afkapwaarde voor MR-proADM bij patiënten met COPD gekozen voor de mediaan van de populatie. In hoofdstuk 2 hebben we ook geprobeerd het beste afkappunt in stabiele fase te vinden voor MR-proADM om mortaliteit te voorspellen. Het beste afkappunt hangt af van het beoogde gebruik en de onderzochte populatie. Om te weten of MR-proADM gebruikt kan worden voor het stratificeren van risico's in de klinische praktijk, moeten we het gedrag ervan in de loop van de tijd kennen. Omdat COPD een onstabiele ziekte is en markers in de loop van de tijd binnen patiënt kunnen variëren, is het interessant om te weten hoe het verband en voorspellende waarde van MR-proADM met mortaliteit en morbiditeit zich gedraagt wanneer er een serie gestandaardiseerde metingen wordt gedaan bij één patiënt in de loop van de ziekte. Het gebruik van een biomarker voor het selecteren van de juiste behandeling is ook een interessant onderwerp. In het huidige proefschrift laten we zien hoe deze biomarker gerelateerd is aan ziekte mortaliteit en morbiditeit. Het wijzigen van het type behandeling of de intensiteit van de behandeling afhankelijk van de waarde van de biomarker zou de volgende stap zijn.

Tot slot, voordat MR-proADM kan worden gebruikt om ziekteprogressie en respons op therapie te volgen, zullen verdere studies moeten onderzoeken of MR-proADM waarden veranderen door behandeling (farmacologisch en/of niet-farmacologisch) van COPD.

Medical School Twente

Calling and comradeship
Unravelling the essence of physician performance

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
vrijdag 12 juni 2020 om 14.45 uur

door

Myra Petronella Gertruda van den Goor
geboren op 23 december 1970
te Heerlen

Promotoren:	prof. dr. J.A.M. van der Palen
	prof. dr. T. Bondarouk
Copromotor:	dr. B.J. Thio

Samenvatting

Achtergrond

Goed functionerende dokters zijn essentieel voor het leveren van patiëntenzorg op hoog niveau. Tegenwoordig is het voor medisch specialisten een behoorlijke uitdaging om goed te blijven presteren in een tijd van steeds veranderende gezondheidszorgsystemen, marktwerking en toenemende bureaucratie. Ondanks deze continu veranderende en dynamische condities, functioneert de grote meerderheid van de medisch specialisten op een hoog niveau. Hoe doen ze dat? Ik vroeg me af wat 'makes doctors tic' en dus heb ik geprobeerd om in dit proefschrift het antwoord te vinden op de vraag wat de kern is van het functioneren van medisch specialisten. Omdat men tegenwoordig vooral in teams werkt in plaats van individueel, worden de onderlinge interactie en de connectie tussen de medisch specialisten belangrijke aspecten als het om functioneren van het individu gaat. Met mijn onderzoek hoop ik kennis toe te voegen die kan helpen om dokters te ondersteunen zodat zij de beste zorg kunnen -blijven- leveren.

Het streven van dit proefschrift was om erachter te komen wat voor medisch specialisten precies de kern is van goed functioneren. Ten eerste heb ik onderzocht welk effect contact met directe collega's heeft op het functioneren van de individuele medisch specialist. Verder heb ik geëxploreerd wat dokters eigenlijk zelf verstaan onder goed functioneren. Het doel van dit proefschrift was om het thema functioneren van medisch specialisten te onderzoeken, vandaar de logische keuze om dokters zelf om antwoorden te vragen. Ik heb me volledig gebaseerd op hun verhalen, reflecties, gevoelens, standpunten en meningen. Kortom, ik heb de dokter in mijn wetenschappelijke spotlight gezet, wat geresulteerd heeft in zes verschillende onderzoeksprojecten.

Bij het verbinden van deze zes projecten, ontstonden twee overkoepelende thema's die de kern van goed functioneren vormen: Kameraadschap (positieve en steunende relatie met directe collega's gebaseerd op wederzijds vertrouwen, veiligheid en verantwoordelijkheid voor elkaar) en Roeping (het hebben van werk dat een gevoel van zingeving of betekenisgeving oproept en waarbij je anderen helpt).

Kameraadschap

In mijn zoektocht naar het effect van contact met directe collega's op het functioneren van de individuele medisch specialist, ontstond het begrip kameraadschap als essentiële component om goed te kunnen functioneren en dus behorende tot de kern van het dokter zijn. De algemene conclusie van onze bevindingen wijst erop dat medisch specialisten het hebben van een veilige en steunende omgeving niet alleen ondersteunend vinden voor het functioneren van het individu, maar dat ze het zien als een essentieel onderdeel om als individu optimaal te kunnen functioneren. De individuele dokter kan alleen echt tot bloei komen in een omgeving met een samenwerkings-mindset, waar het gaat over delen, zorgen voor elkaar, wederzijds vertrouwen, waar een gevoel van eenheid en onderlinge steun aanwezig is.

Deze conclusies zijn gebaseerd op vier verschillende onderzoeksprojecten, ieder met een eigen invalshoek en analytisch proces. In **hoofdstuk 2** startte ik aan de 'slechte' kant van het functionerings-spectrum namelijk disfunctioneren. Het is aannemelijk dat situaties waar relaties onder druk staan, waardevolle informatie geven over hoe collega's met elkaar omgaan. Tien elektronische databases zijn geanalyseerd, 25 tuchtzaken bekeken en 12 experts geïnterviewd. De uitkomsten van dit onderzoek lieten zien dat een matig gevoel van kameraadschap (vertaald in slechte samenwerking en onvoldoende feedback geven en aanspreken), een vruchtbare grond is voor functioneringsvraagstukken en dat onder deze omstandigheden disfunctioneren kan ontstaan. Deze bevinding onderstreept de noodzaak om een cultuur te creëren waarin aangesproken kan worden en 'blame-free' discussies over functioneren mogelijk zijn. Om zo'n cultuur te creëren en de drempel om elkaar aan te spreken te verlagen, helpt het om geregeld het eigen functioneren in de groep te bespreken. Deze bevindingen onderstrepen dat het individuele functioneren altijd een samenspel is van het individu en zijn of haar omgeving. Dus functioneringsvraagstukken moeten altijd in een breder perspectief geplaatst worden in plaats van gezien worden als een individuele kwestie.

Van disfunctioneren gingen we naar het detecteren van zogenaamde 'soft signals' in de tweede studie (**hoofdstuk 3**). Geïnterviewde medisch specialisten gaven aan dat zij als geen ander als eerste afwijkingen ontdekken in verandering van gedrag, communicatie of verschijning van een collega. Dokters voelen zich sterk medeverantwoordelijk voor het welzijn van hun collega's, een duidelijk voorbeeld van kameraadschap. In deze studie bleek dat dokters voor elkaar willen zorgen door actief signalen of zorgen op te pikken en de helpende hand te bieden. Om een cultuur van kameraadschap en aanspreken te stimuleren, helpt het om standaard het individueel- en groeps-functioneren te bespreken, en om daarbij vooral de positieve aspecten zoals inspiratie en ambitie niet te vergeten.

Dat een psychologisch veilige cultuur simulerend werkt op het geven en ontvangen van feedback op het functioneren, toonden we aan in **hoofdstuk 4**. We onderzochten de link tussen psychologische veiligheid en feedback op functioneren. Het bleek dat men in een psychologisch veiligere omgeving positiever staat tegenover het geven en krijgen van feedback. De conclusie is, dat het van belang is als groep om te investeren in goede onderlinge relaties. Dat kan onder andere door teambuildingsactiviteiten, het verkrijgen en bespreken van 360° feedback en het ondernemen van sociale activiteiten. Daarnaast is het elkaar bijstaan in geval van complicaties of, nog erger, tuchtzaken erg belangrijk voor de onderlinge verbondenheid. Ook een zogenaamde inclusieve leiderschapsstijl werkt stimulerend: de ander uitnodigen om iets te zeggen, expliciete waardering geven en proactief vragen naar andere meningen.

Constructieve collegiale relaties zijn van cruciaal belang voor de professionele ontwikkeling en het functioneren van de individuele medisch specialist. Om goede kwaliteit van zorg te borgen, moeten alle medisch specialisten periodiek aantonen dat ze aan alle vigerende voorwaarden voldoen. Onderdeel van dit proces is aandacht besteden aan het individuele functioneren middels 360° feedback. In **hoofdstuk 5** wordt de verbinding gemaakt tussen functioneren van het individu en de groep, door de potentiële meerwaarde te onderzoeken van

groepsgewijze reflectie op het individuele functioneren. Deze studie laat zien dat ‘sharing is caring’; groepsgewijs reflecteren geeft de mogelijkheid om te discussiëren en de eigen perceptie te vergelijken met die van de collega’s. Gezamenlijk reflecteren levert voor het individu een verfijnder beeld op van het eigen functioneren. Dokters ervoeren het delen als een vorm van collegiale steun en het verdiepte gemeenschappelijke verbondenheid op groepsniveau. Op het individuele niveau hielp het delen om daadwerkelijk verandering te realiseren en het creëerde een gevoel van urgentie om tot verandering te komen. De bevindingen laten dus een positief effect zien op zowel individueel- als groepsniveau alsmede de hechte samenhang tussen individu en groep waar het ontwikkeling en functioneren betreft. Hieruit concludeer ik dat functioneren niet op individueel niveau bezien dient te worden, de context van het individu hoort er altijd bij betrokken te worden.

Alhoewel de twee studies uit **hoofdstuk 6** en **hoofdstuk 7** primair ontworpen waren om antwoord te geven op de vraag wat dokters zelf verstaan onder goed functioneren, leverde deze onderzoeken ook informatie op betreffende het thema kameraadschap. **Hoofdstuk 6** toonde het negatieve effect van slechte onderlinge relaties waarbij medisch specialisten aangaven dat een slechte sfeer binnen de groep hun welzijn en functioneren belemmerde. Sommigen overwogen zelfs een betrekking elders vanwege samenwerkingskwesties. In **hoofdstuk 7** verklaarden medisch specialisten aspecten als onderlinge cohesie, wederzijds vertrouwen en een positieve steunende omgeving van essentieel belang om goed te kunnen functioneren als individu.

Roeping

In de zoektocht naar het ontrafelen van de kern van goed functioneren, heb ik me vervolgens gericht op de individuele medisch specialist en geëxploreerd wat dokters eigenlijk zelf verstaan onder goed functioneren. Daaruit blijkt dat medisch specialisten enorm toegewijd zijn aan hun patiënten en dat ze medemenselijkheid beschouwen als het hart van dokter zijn. Vandaar dat de term ‘roeping’ (het hebben van werk dat een gevoel van zingeving of betekenisgeving oproept en waarbij je anderen helpt) als tweede essentiële component ontsproot, om goed te kunnen functioneren als individu en dus behorende tot de kern van het dokter zijn. De algemene conclusie van deze bevindingen duiden dat dokter zijn wordt ervaren als werk dat diepe voldoening geeft, het gevoel ertoe te doen, waarbij motivatie en inspiratie voortkomen uit de toewijding om de patiënt zo goed mogelijk te helpen. Roeping, toewijding en medemenselijkheid waren centrale thema’s in de twee onderzoeken naar de perceptie van dokters met betrekking tot goed functioneren (**hoofdstuk 6** en **hoofdstuk 7**). Mijn analyse van bijna 800, door dokters geschreven, reflecties laat zien dat voor de medisch specialist de arts-patiënt relatie de kern vormt als het gaat over functioneren. Ze zijn van mening dat alle andere activiteiten uit dit medemenselijke contact voortvloeien. Deze activiteiten vertalen zich in praktische zin in het streven naar het beste doen voor de patiënt. Om het beste te kunnen doen, is volgens medisch specialisten nodig om bij te blijven qua kennis en vaardigheden, kennis en kunde te delen, verantwoordelijkheid te nemen en transparant te zijn.

Uit interviews met 28 medisch specialisten en 7 HR professionals ontstond het beeld van de dokter als zeer toegewijde en bezielde professional, die te allen

tijde die extra stap willen doen voor hun patiënten (Hoofdstuk 7). Deze toewijding bleek ook uit het feit dat vele dokters aan het interview deelnamen buiten de gewone werktijd, omdat ze wilden bijdragen aan vooruitgang, ondanks de hoge werkdruk en beperkte tijd. In hun opinie was deze toewijding niet slechts een antecedent voor goed functioneren, zoals het wordt beschreven in de meeste onderzoeken, maar een cruciaal element om optimaal te kunnen functioneren. Gebaseerd op deze bevindingen, concludeerde ik dat toewijding, passie, verbondenheid en intrinsieke motivatie het gevoel van zingeving vormen van de roeping van dokters; concepten die allemaal met elkaar vervlochten zijn en positief gerelateerd aan goed functioneren. De bevindingen van het laatste onderzoek onderstrepen dit nog nadrukkelijker aangezien daaruit blijkt dat passie en ambitie integraal onderdeel uitmaken van de dokterscultuur en dat deze bril bepalend is voor hoe medisch specialisten naar functioneren kijken.

Medemenselijkheid komt voort uit toewijding, passie en ambitie en vormt de kern van het dokter zijn. Het lijkt erop dat het huidige meer zakelijke klimaat binnen de gezondheidszorg de medemenselijke zorg onderdrukt. De resultaten laten zien dat medisch specialisten de toenemende en zware administratieve werklast ervaren als een serieuze bedreiging voor hun eigen functioneren. Dit heeft vooral een negatief effect op hun roeping als dokter en op de tijd en aandacht die ze aan hun patiënten kunnen en willen besteden (hoofdstuk 6). De medisch specialisten in mijn onderzoeken staven bevindingen van andere studies dat de toenemende registratielast leidt tot een vermindering van face-to-face contact met patiënten. Juist datgene inperken wat dokters in het bijzonder inspireert en enthousiasmeert, zal er uiteindelijk toe leiden dat dokters de tijd, energie en motivatie zullen gaan missen om de best mogelijke zorg te leveren.

Aanbevelingen
De belangrijkste les die uit dit proefschrift geleerd kan worden, is dat medisch specialisten door de lens van roeping en kameraadschap naar hun functioneren kijken. Voor dokters draait het allemaal om toewijding aan de patiënt, passie, motivatie, ondersteuning door collega's, wederzijds vertrouwen en een veilig gevoel. Mijn bevindingen suggereren dat medisch specialisten alleen kunnen floreren in een omgeving die deze mens- en relatiegerichte waarden erkent en versterkt. Echter, de huidige verzakelijking in de gezondheidszorg richt de spotlight op proces, regels, verantwoording en efficiency. Aspecten die populairder zijn geworden in een periode waarin het vertrouwen in de medische professie vanuit de samenleving is afgenomen door het vóórkomen incidenten waardoor de roep om meer transparantie, verantwoording en meetbare uitkomsten is ontstaan.

Gebaseerd op mijn bevindingen pleit ik er sterk voor om deze verzakelijking tegen te gaan, door mensen centraal te zetten, boven proces en productiviteit. De resultaten van dit proefschrift vertegenwoordigen een wetenschappelijk argument voor een bredere maatschappelijke roep tot verandering om de hedendaagse verzakelijkte gezondheidszorg weer te 'verzachten'.

Aanbevelingen voor de individuele medisch specialist
Om bezield je werk te kunnen doen als dokter en collega, is het nodig om goed te zorgen voor jezelf en voor diegene om je heen. Zelfzorg zou dus beschouwd

kunnen worden als onderdeel van professioneel gedrag. Om optimaal te kunnen presteren, is goed zorgen voor je eigen fysieke en mentale welzijn namelijk een belangrijke voorwaarde. Verder blijkt uit dit onderzoek dat medisch specialisten behoefte hebben aan het bijschaven van kennis en kunde op het gebied van leiderschaps- en samenwerkingsvaardigheden. Een behoefte waar in post academische trainingen kan worden voorzien. Waar het leiderschap betreft, blijkt de zogenaamde 'inclusieve leiderschapsstijl' een positief effect heeft op de kwaliteit van de onderlinge relaties. Gedrag dat hier bij past: collega's nadrukkelijk uitnodigen om iets te zeggen, expliciete waardering tonen, proactief om andere meningen vragen, een helpende hand bieden, reflecteren op en zelf geven van feedback, delen van ervaringen en zelf open durven zijn. Zo'n houding zou door iedere dokter uitgedragen kunnen worden, ongeacht een al dan niet formele leiderschapspositie. Medisch leiderschap 2.0 staat voor (zelf)reflectie en eigenaarschap van alle actoren, om zo bij te dragen aan sociale cohesie en vergroten van welzijn, werk- en geneesplezier.

Aanbevelingen op groepsniveau

Individuen kunnen alleen floreren in een cultuur waarin vertrouwen en veiligheid gevoeld wordt. Vandaar dat investeren in zo'n cultuur essentieel is, zeker aangezien de afwezigheid van psychologische veiligheid vaak resulteert in ontregeling van de samenwerking. Groepen kunnen investeren in zo'n cultuur door periodiek met elkaar te discussiëren over en reflecteren op het individuele- en groepsfunctioneren. Groepsgewijs reflecteren bevordert de professionele ontwikkeling en het functioneren, verlaagt de drempel om aan te spreken en creëert de mogelijkheid om elkaar te adviseren en helpen. In Nederland worden deze voordelen, binnen de context van herregistratie, in toenemende mate herkent en wordt groepsgewijs reflecteren meer gemeengoed. In zijn algemeenheid zouden groepen en afdelingen aandacht moeten besteden aan het optimaliseren van de onderlinge verbondenheid aangezien het is bekend dat je dan bouwt aan vertrouwen in een team. Het versterken van de onderlinge cohesie kan door middel van verschillende activiteiten zoals gezamenlijk discussiëren over ingrijpende gebeurtenissen of fouten en elkaar steunen in zulke omstandigheden, medisch inhoudelijke onderwerpen bespreken met elkaar en teambuildings activiteiten. Naast de werk context zijn sociale activiteiten ook van belang om de onderlinge banden te optimaliseren. Verder zouden teams gebruik moeten maken van de unieke talenten en drijfveren van de individuen binnen hun groep aangezien het inzetten op kwaliteiten leidt tot beter presteren.

Aanbevelingen op organisatie niveau

Vanwege de sterke link met kwaliteit van zorg en patiënt veiligheid, is het hebben en houden van betrokken en op samenwerking gerichte dokters essentieel voor gezondheidszorg organisaties. Om toegewijde medisch specialisten in toegewijde teams te stimuleren, zouden organisaties moeten investeren in een op samenwerking gerichte mentaliteit. Dat kan onder andere door groepen en afdelingen te faciliteren om aan de onderlinge verbondenheid te werken. Aangezien de raad van bestuur en medische staf gezamenlijk verantwoordelijk zijn voor de kwaliteit en het welzijn van haar specialisten, hebben zij een verantwoordelijkheid om ervoor te zorgen dat groepen gefaciliteerd worden om tijd aan het team te besteden. Investeren in de groep zou niet optioneel moeten zijn en ook niet alleen de verantwoordelijkheid van de groep zelf. Een op

samenwerking gerichte mentaliteit kan versterkt worden door formele peer-support of coachings programma's op te zetten, te investeren in multidisciplinaire samenwerking en in gezamenlijk reflecteren op (groeps) functioneren, gevolgd door begeleiding en steun indien nodig. Medisch specialisten hebben te maken met unieke uitdagingen (zoals medisch fouten en tuchtzaken) en ze hebben een professionele identiteit en rol die duidelijk anders is dan andere disciplines. Vandaar dat directe collegiale steun van oudsher een belangrijke manier is voor dokters om met dit soort situaties om te gaan. Het onderwerp peer-support staat in de belangstelling en formele programma's rond dit thema zijn inmiddels in vele ziekenhuizen geïmplementeerd. Echter, de meer informele onderlinge contacten en wisselwerking zijn steeds meer beperkt door een op productie gedreven, tijd en middelen effectieve mentaliteit. Deze mentaliteit heeft geleid tot het afbrokkelen van onderlinge steun en een groter gevoel van eenzaamheid voor vele medisch specialisten.

In een poging om dit tij te keren, kan een voorbeeld genomen worden aan de Mayo Clinics, waar speciale ontmoetingsplaatsen zijn gecreëerd voor dokters, met fruit, drinken, computers en lunch tafels. Deze plekken stimuleren een gemeenschappelijk gevoel en een gevoel van kameraadschap. Een ander initiatief is het financieren van een lunch waarbij kleine groepen dokters discussiëren over het voorrecht en de uitdagingen van het dokter zijn. Deze bijeenkomsten leiden tot een stimulans wat betreft zingeving en werkplezier, alsmede daling van burn-out.

Tegenwoordig lijkt elke ontmoeting zo efficiënt mogelijk te moeten zijn. Met dit bijproduct van de huidige verzakelijking in de zorg, worden de voordelen van het organisch tijd doorbrengen met elkaar, het delen met en helpen van collega's, overschaduwd. Om dit te herstellen en een gezonde balans te verkrijgen, zouden zulke ontmoetingen weer plaats moeten vinden. En als dat niet organisch gebeurt, dan maar geïnstitutionaliseerd.

Medical School Twente

Health promoting effects of nutrition in children
The clinical effects of a dietary advice consisting of beef, green vegetables, whole milk and butter

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
woensdag 18 maart 2020 om 14.45 uur

door

Ellen José Van Der Gaag - Heuvel

Promotoren: prof. dr. J.A.M. van der Palen
Copromotor: dr. T.Z. Hummel

Samenvatting

Dit proefschrift is ontstaan door het ontbreken van therapieën voor alledaagse lichamelijke klachten en problemen die ik als kinderarts tegenkwam. Veel voorkomende problemen zoals steeds terugkerende luchtweginfecties (het chronisch verkouden zijn), vermoeidheid, aspecifieke allergieën, een verstoorde maar nog net redelijk goed functionerende schildklier hebben vaak geen medische verklaring. Door het ontbreken van een medische verklaring, houdt het ook in dat er geen therapie voorhanden is, en dat je als arts niet iets kan bieden aan de ouders. In onze onderzoeken hebben we onderzocht of een voedingsadvies een mogelijke behandeling kan zijn, aangezien grote groepen kinderen niet alle voedingsstoffen binnenkrijgen en een aanzienlijk percentage kinderen (met name de kinderen die kwakkelen) minder dan één keer per week groente eet. Wij ontwikkelden hiervoor een voedingsadvies met onbewerkte producten; 5x per week groene groenten bij de avondmaaltijd, 3x per week rundvlees bij de avondmaaltijd, dagelijks 300 ml volle zuivel (volle melk of volle yoghurt) en roomboter op brood. Alles in leeftijdsadequate hoeveelheden volgens het voedingscentrum. De achtergronden en het ontstaan van het voedingsadvies worden beschreven in **hoofdstuk 1**.

Hoofdstuk 2 beschrijft een overzicht van uitkomsten van reeds gepubliceerde literatuur (een review) over de effecten van verschillende soorten voeding op luchtweginfecties bij kinderen en volwassenen. De resultaten van andere onderzoekers suggereren gunstige effecten van voeding bij het voorkomen en verkorten van de duur van infecties van de bovenste luchtwegen. De voedingsproducten die dit kunnen bewerkstelligen zijn bijvoorbeeld; kiwi, vlierbessen, pre- en probiotica, visolie en knoflook.

Bij patiënten met terugkerende infecties van de bovenste luchtwegen kan een advies met één enkel voedingsproduct dus gunstig zijn. Een dieetinterventie met meerdere voedingsproducten voor luchtweginfecties is zelden onderzocht, met uitzondering van de effecten van het mediterrane dieet in Spanje. In dit voor-na onderzoek werd een afname van luchtweginfecties vastgesteld na een verandering in de leefstijl (combinatie van mediterrane eetgewoontes en lichamelijke beweging). De effecten van het mediterrane dieet zijn gebaseerd op het concept van voedselsynergie; de effecten van (een combinatie van) voedsel zijn veel sterker zijn dan de effecten van het aanvullen van een enkele voedingsstof of product (zoals bv het aanvullen van vitamine C of alleen kiwi). Door de synergie heeft het meerdere aangrijpingspunten waarbij het de afweer kan versterken. Sommige mechanismes zijn al bekend, maar er zijn ook nog niet ontdekte mechanismes.

Hoofdstuk 3 beschrijft de effecten van ons dieetadvies, bestaande uit rundvlees (3 keer per week), groene groenten (5 keer per week), dagelijkse 300 ml volle melk en roomboter, op het IgE-gehalte bij kinderen met luchtwegklachten. Een verhoogd IgE gehalte wordt o.a. gevonden bij allergieën. In deze retrospectieve case-control studie bij 105 kinderen zagen we een daling van het IgE gehalte van 9,2 kU/l (=22 ug/l) na 4 maanden volgen van het voedingsadvies. We hebben geen verandering in de IgE-gehaltes in de controlegroep waargenomen. Bij 53% van de kinderen in de voedingsadviesgroep en 29% in de controlegroep ($p<0.001$) werden subjectieve verbeteringen van de klinische klachten genoemd door de ouders.

In **hoofdstuk 4** hebben we het effect van hetzelfde voedingsadvies op de vermoeidheid bij kinderen onderzocht. In dit niet-gerandomiseerde gecontroleerde onderzoek bij 98 kinderen met onverklaarde vermoeidheidsverschijnselen verbeterde de slaap in de interventiegroep (de voedingsgroep). We evalueerden elk afzonderlijk voedingsbestanddeel (van de vier in totaal) en het effect daarvan op de vermoeidheid in de onderzochte populatie. Groene groenten verbeterden de cognitieve vermoeidheidsscores significant en volle melk verbeterde het slaapdomein significant.

Het Lipidenprofiel (cholesterol spectrum) wordt nauwelijks onderzocht bij jonge kinderen wanneer er geen relatie is met familiaire dyslipidemie (een aangeboren aanleg voor afwijkingen in de cholesterol stofwisseling). Het grootste gedeelte van de kinderen heeft dat niet. Wat zijn de gevolgen voor het lipidenprofiel wanneer kinderen zonder deze afwijking volvette zuivelproducten in hun dieet introduceren? In **hoofdstuk 5** zijn de resultaten beschreven van een retrospectieve case-control studie op de lipidenprofielen van kinderen met en zonder het voedingsadvies. Na 5 maanden liet de voedingsadviesgroep geen ongunstige lipidenprofielen zien. Integendeel, HDL-cholesterol (een prognostische gunstige risicofactor voor hart- en vaatziekten) nam na het volgen van het voedingsadvies aanzienlijk toe, evenals de cholesterol/HDL-verhouding en het niet-HDL-cholesterol. Alle drie de waardes veranderden naar de gunstige richting. Er werden geen ongunstige trends in de lipidenprofielen waargenomen. Ook werden de BMI- en BMI-z-scores niet negatief beïnvloed door de introductie van volvette zuivelproducten in combinatie met groene groenten en rundvlees.

Als onderdeel van dit proefschrift werd een gerandomiseerde gecontroleerde dieetinterventie uitgevoerd met een dieetverandering bij 118 jonge kinderen (1-4 jaar) met terugkerende infecties van de bovenste luchtwegen. Ook hier hebben we het voedingsadvies bestaande uit groene groenten, rundvlees, volle melk en roomboter gedurende 6 maanden geëvalueerd. We vonden een significante afname in infectiedagen, verkoudheid episodes, hoesten en dagen met koorts. Ook het antibioticagebruik daalde met 66,6% over een periode van 6 maanden (**hoofdstuk 6**). Er werd geen significante gewichtstoename of verhoging van de BMI gezien in de interventiegroep.

Vermoeidheidsscores verbeterden in onze tweede gerandomiseerde studie bij kinderen met een subklinische hypothyreoïdie, na het volgen van het voedingsadvies voor 6 maanden (**hoofdstuk 7**). Als we kijken naar de verschillende vermoeidheidsdomeinen, verbeterden vooral de domeinen van de slaap en de totale vermoeidheidsscore. De functie van de schildklier, uitgedrukt in de waarden van TSH en FT4, werd niet beïnvloed door het voedingsadvies. In deze studie konden we geen effect van groene groenten op de cognitieve vermoeidheid vinden (wat we wel in hoofdstuk 4 gevonden hebben), waarschijnlijk omdat in de huidige studie onze controlegroep aanzienlijke hoeveelheden groene groenten consumeerde en het verschil tussen beide groepen voor de inname van groene groentes minder groot was.

Effecten van het voedingsadvies op laboratoriumparameters

Luchtweginfecties
Na het volgen van de dieetinterventie gedurende 6 maanden in de gerandomiseerde luchtweginfectie studie hebben we geen significante veranderingen in laboratoriumparameters tussen de groepen waargenomen, met uitzondering van de CRP-waardes. Deze waardes werden significant verlaagd in de interventiegroep in vergelijking met de controlegroep, wat mogelijk wijst op een lagere chronische ontsteking. Deze bevinding moet echter wel in perspectief gezien worden, aangezien de waardes nog steeds in het normale bereik liggen (**hoofdstuk 6**).

Binnen de interventiegroep werden na 6 maanden significante veranderingen gevonden ten opzichte van dezelfde laboratoriumparameters bij de start van het onderzoek. Ook in de controlegroep werden enkele veranderingen gezien. Significante veranderingen die alleen in de interventiegroep werden gevonden waren; toegenomen gemiddeld corpusculair volume (MCV), verminderde leukocyten, verlaagd ferritine, verlaagd IgM en toegenomen IgE. Sommige parameters suggereerden een verminderde immunologische activiteit (leucocyten, ferritine (aangezien ferritine significant gecorreleerd was met de CRP-waardes), en IgM). Verrassend genoeg werden IgE waardes verhoogd na 6 maanden in onze RCT in zowel onze interventiegroep en controlegroep met 25.0 en 24.9 ug/l, respectievelijk. Het absolute verschil in IgE-waardes tussen de interventie- en controlegroep was minimaal, hoewel het statistische verschil in de interventiegroep significant was door een lagere standaardafwijking (106 in de interventiegroep ten opzichte van 148 in de controlegroep). Deze bevinding was deels tegenstrijdig aan de bevinding van de verlaagde IgE-waardes in een case-control studie (**hoofdstuk 3**). In de retrospectieve case-control studie verdween het effect van het voedingsadvies door suppletie van vitamine D. In de gerandomiseerde gecontroleerde studie zijn de kinderen tussen de 1 en 4 jaar oud. Het landelijke advies in deze groep is om vitamine D te gebruiken. In de laatste studie is vitamine D dan ook geen confounder. Op dit moment kunnen we de bijdrage van de voedingsinterventie aan een allergische constitutie niet inschatten. We hebben geconstateerd dat de waarden van IgE aanzienlijk uiteenlopen met enkele uitschieters, wat de interpretatie van de resultaten bemoeilijkt.

Schildklier en vermoeidheid
We zagen geen effecten op het functioneren van de schildklier na de dieetinterventie in onze gerandomiseerde studie in patiënten met subklinische hypothyreoïdie. Ft4, TSH noch anti-TPO niveaus veranderden significant (**hoofdstuk 7**). Daarom heeft de voedingsinterventie geen meetbaar effect gehad op de schildklier. Klinische verbeteringen van de vermoeidheid (vergelijkbaar met die in **hoofdstuk 4**) werden gezien, maar deze stonden los van de werking van de schildklier.

Lipiden profiel
Tijdens onze contacten met ouders werd vaak door ouders de angst uitgesproken voor het cholesterol (lipidenprofiel) van hun kinderen als ze een dieetadvies met volle zuivelproducten gaan eten. In al onze onderzoeken zagen we een consistente trend in het lipidenprofiel na het volgen van het voedingsadvies. Prognostisch gunstige HDL-waarden stegen in alle 3 de studies (zowel in de gerandomiseerde studies als de case control studie, **hoofdstuk 5,6 en 7**) en ook de cholesterol/HDL-verhouding daalde naar prognostische gunstige waarden (alle 3 de studies). Het totale

cholesterolgehalte en LDL bleven gelijk of namen licht toe. Triglyceriden zijn sterk afhankelijk van de laatste ingenomen maaltijd. Deze bleven gelijk, stegen of daalden; in elke studie in een andere richting. Een verschil in de afgelopen jaren is het moment van het bloedprikken voor de laboratoriumtesten. In het begin moesten de patiënten nuchter komen, maar in de afgelopen jaren was dit op elk moment van de dag mogelijk, niet gerelateerd aan een nuchtere maag. Deze instructies werden door het laboratorium gegeven. Mogelijk dat dit de veranderingen in triglyceriden kan verklaren.

Groei
In beide gerandomiseerde gecontroleerde studies (**hoofdstuk 6 en 7**) hebben we metingen verricht naar de groeiparameters, voornamelijk vanwege de angst voor overgewicht bij het starten van volle zuivelproducten in het dieet.
In beide gerandomiseerde studies zagen we geen significante veranderingen in de groei. Ook zagen we geen ongunstige trends; na 6 maanden follow-up bleef de lengtegroei in beide controlegroepen gelijk, maar steeg de lengtegroei iets meer in beide interventiegroepen (d.w.z. Een deel gewone groei en een minimaal deel inhaalgroei). Dit zijn kleine veranderingen in een relatief korte periode, follow-up studies moeten verricht worden of dit een klinische betekenis heeft.

Wat betreft de body mass index (BMI), in de controlegroep steeg de BMI na 6 maanden met 0,27 SD in de luchtweginfectie-studie en 0,01 SD in de schildklier-studie. Na de dieetverandering naar volle zuivelproducten steeg de BMI met 0,04 SD in de URTI-studie en met 0,06 SD in de SH-studie. Dit suggereert geen effect van volle zuivelproducten in combinatie met rundvlees en groene groenten op de BMI bij kinderen.

Conclusie
Naar aanleiding van onze onderzoeken adviseren wij het door ons onderzochte voedingsadvies aan Nederlandse kinderen met luchtweginfecties zonder immunologische afwijkingen of vermoeidheid zonder medische verklaring. Een dieet met groene groenten, rundvlees, volle melk en roomboter resulteert in minder luchtwegklachten bij jonge kinderen en minder vermoeidheid. Dit kan te wijten zijn aan gunstige bestanddelen van het voedingsadvies of aan de eliminatie van ongezonde voedingsbestanddelen zoals transvetzuren, die nu vaak aanwezig zijn in de voeding van kinderen. Elk voedingsproduct heeft zijn eigen kwaliteiten en effecten op de menselijke gezondheid en meerdere voedingsproducten kunnen elkaar aanvullen en met elkaar reageren. Door de combinatie van meerdere producten kunnen er bredere effecten in gang gezet worden in plaats van de effecten van één enkel (superfood)voedsel.

Het onderzochte dieet bestaat voornamelijk uit onbewerkt voedsel, en componenten van een traditioneel Nederlands dieet. Deze componenten kunnen worden verwerkt in de mediterrane, Aziatische of andere keuken, al naar gelang de eetgewoontes van het gezin. Zelfs als ze verschillend verwerkt worden, kunnen de componenten nog steeds voldoen aan de ingrediënten van ons onderzochte dieet, en de gezondheid van kinderen bevorderen.

Neurologie

EEG biomarkers in depression paving the way for stratified psychiatry

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 graduation committee,
to be publicly defended
on Wednesday, the 1st of July 2020, at 16:45 hrs.

by

Nikita van der Vinne
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Supervisor: Prof. dr. ir. M.J.A.M. van Putten

Co-supervisors: Dr. M.W. Arns
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Samenvatting
Bij een depressieve stoornis horen een aantal symptomen, waaronder een depressieve stemming gedurende een groot gedeelte van de dag (bijna elke dag), verlies van interesse in alledaagse activiteiten, gewichtstoename of dieet-onafhankelijk gewichtsverlies, vermoeidheid, en het gevoel van waardeloosheid of schuld (zoals beschreven in de Diagnostic and Statistical Manual of Mental Disorders 5). Deze stemmingsstoornis wordt gekenmerkt door een langdurig verloop, dat in veel gevallen uiteindelijk een chronisch probleem wordt. Na een lange geschiedenis van beschrijven, verklaren en behandelen van de stoornis, lopen patiënten en hun behandelaren nog altijd aan tegen de uitdaging om de stoornis aan te pakken, ondanks het vele onderzoek.

Depressie wordt doorgaans behandeld met antidepressiva (AD) of psychotherapieën zoals cognitieve gedragstherapie. Klinische effectiviteit gemeten door remissie, laat echter percentages zien van ten hoogste 37% remissie na een eerste AD, waarna dit percentage zakt na elke opvolgende poging met een AD. De grote (en nog altijd groeiende) wereldwijde depressieprevalentie is verontrustend: 183 miljoen mensen kregen een depressie in 2005, tot aan 216 miljoen in 2015. De ontwikkeling van nieuwe antidepressiva is momenteel grotendeels stilgelegd, budgetten voor dergelijk onderzoek zijn er nauwelijks meer. Omdat een groeiende groep mensen is aangedaan door deze stoornis, zijn er nieuwe vormen van onderzoek nodig om deze groep te bedienen.

Met het doel om de behandeluitkomst voor depressieve patiënten te verbeteren, hebben we in dit proefschrift onze eerste stappen beschreven naar de implementatie van een protocol gebaseerd op EEG-biomarkers. Een biomarker is een meting in het lichaam die informatie geeft over of een persoon een ziekte heeft, of voor het bepalen van de juiste behandeling. Het elektro-encefalogram (ofwel EEG), meet elektrische activiteit in de hersenen door elektroden. In onze studies legden we de focus op de gedetailleerde eigenschappen van veelbelovende biomarkers. We probeerden gebruik te maken van geautomatiseerde processen voor snelle en geprofessionaliseerde EEG-verwerking. We ontwikkelden een protocol waarin alle kennis over het voorschrijven van AD's gebaseerd op EEG-biomarkers werd geïmplementeerd, en voerden een haalbaarheidsstudie uit. We vergeleken hierbij ook de uitkomst van ons protocol met de resultaten van een controlegroep.

Hoofdstuk 2 geeft een actuele meta-analyse van de diagnostische waarde van de biomarker frontale alfa asymmetrie (FAA) voor depressie. Ook worden de verschillen en afwijkingen in een grote cross-sectionele dataset geëvalueerd. Zestien studies werden geïncludeerd (depressie: n = 1883, controles: n = 2161). Het hoofdresultaat was een niet-significante, verwaarloosbare effect size, wat aantoont dat FAA weinig diagnostische waarde heeft in depressie. De hoge mate van heterogeniteit in de verschillende studies geeft aan dat er invloed is van andere factoren (covariabiliteit), wat bevestigd werd met cross-sectionele analyses.

Hoofdstuk 3 verkent de stabiliteit van de biomarker FAA, wat al eerder is aangetoond in kleine studies. In depressiepatiënten veranderde FAA niet na acht weken medicatie (n = 453, p = .234). Ook vonden we geen relatie met leeftijd, geslacht, de ernst van de depressie, of verandering in de ernst van de depressie. We tonen hiermee aan dat FAA een stabiele eigenschap is (trait), die niet veel beïnvloed

kan worden door tijd, de toestand van een persoon en medicatie. Dit bevestigt de stabiliteit van FAA.

Hoofdstuk 4 onderzoekt of depressieve patiënten met een licht afwijkend EEG een normalisatie in hun EEG laten zien dat gerelateerd is aan de behandeling met een AD en respons, en of dat effect voorkomt bij één specifiek AD. In 57 patiënten met een afwijkend EEG, normaliseerde het EEG niet méér met sertraline, vergeleken met andere AD's, escitalopram en venlafaxine. Echter, de behandelrespons van patiënten met een genormaliseerd EEG die een behandeling met sertraline kregen was 5,2 keer (significant) hoger dan in patiënten die behandeld werden met escitalopram of venlafaxine.

Hoofdstuk 5 laat zien hoe we verschillende kenmerken in het EEG berekenden met verschillende methodes, voor het verbeteren van het vinden van afwijkingen in EEG's in de depressieve populatie. Deze kenmerken vergeleken we met onze voorgaande methodes gebaseerd op met name visuele beoordeling. Het convolutional neural network (deep learning), de dominante frequentie, en de temporele brain symmetry index registreerden alle drie meer vertraging of afwijkingen in de groep die we visueel al hadden geclassificeerd als het hebben van "lichte" afwijkingen in het EEG, vergeleken met een groep waarin we die afwijkingen visueel niet eerder vonden. Een random forest model dat alle berekende kenmerken bevatte, werd getraind op het voorspellen van behandeluitkomst per AD. Dit model bleek de behandeluitkomst niet te kunnen voorspellen.

Hoofdstuk 6 evalueert de resultaten van een eerste prospectieve haalbaarheidsstudie. De EEG-biomarkers afwijkende EEG activiteit, alfapiek frequentie, en FAA werden prospectief gebruikt voor het voorschrijven van AD's. Zeventig patiënten werden gestratificeerd naar verschillende AD's, gebaseerd op hun biomarkers, 52 patiënten kregen behandeling zoals gebruikelijk. Over het geheel genomen waren zowel de zorgprofessionals als de gestratificeerde patiënten tevreden met het nieuwe protocol. De praktische implementatie bleek voldoende haalbaar te zijn. Er werd significant meer verbetering in symptomen gezien in patiënten die AD's voorschreven kregen op basis van EEG-biomarkers.

Conclusie

De complexiteit van veel verschillen tussen depressieve patiënten (heterogeniteit) maakt het onmogelijk om één behandeling te vinden die voor iedereen werkt. We kunnen deze heterogeniteit echter omarmen door biomarkers te vinden die het mogelijk maken om homogene subgroepen te identificeren, die mogelijk behandeluitkomst kunnen helpen voorspellen. We kunnen meer betrouwbaarheid en kwalitatieve verbetering bereiken door de allernieuwste technieken te gebruiken, alhoewel deze methodes nog verder ontwikkeld moeten worden voordat ze voor patiënten gebruikt kunnen worden. Aan de andere kant zijn er al kwantitatieve methodes die het mogelijk lijken te maken om behandeluitkomst te voorspellen, gebaseerd op frontale alfa lateralisatie en alfapiek frequentie. Gecombineerd met de kwalitatieve beoordeling van EEG-afwijkingen in ons nieuwe protocol, laten de eerste resultaten zien dat er voldoende haalbaarheid is in een klinische setting. Voor zover wij weten, is dit de eerste poging om de behandeling van depressie te verbeteren via deze biomarkers, die niet alleen aantoonde dat het protocol niet slechter is dan reguliere behandeling: patiënten laten een significante verbetering zien in vergelijking

met medicatie zoals door de psychiater voorgeschreven. Ons voorgestelde protocol maakt het daarmee niet alleen mogelijk om onze methodes naar de klinische praktijk te brengen, het draagt ook de belofte van een kleine maar nodige verbetering van onze behandelnormen, in deze nieuwe vorm van neuropsychiatrische gezondheidszorg voor depressie.
Ik hoop dat dit proefschrift nieuw onderzoek bevordert, dat doorgaat met het focussen op het maken van behandelbeslissingen die geïnformeerd zijn door EEG-biomarkers. Onze studies laten veelbelovende resultaten zien, die de weg vrij maken naar gestratificeerde psychiatrie, waarmee een nog altijd groeiende groep mensen met depressie geholpen kan worden.

Thoraxchirurgie

Balancing safety and efficacy of cryoballoon pulmonary vein isolation in the treatment of atrial fibrillation

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 19 juni 2020 om 14:45

door

Marleen Maria Dirkje Molenaar
geboren op 15 februari 1987
te Purmerend, Nederland

Promotoren: Prof. dr. J.G. Grandjean
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Samenvatting
Ablatie door middel van cryoballon therapie heeft zich in het afgelopen decennia ontwikkeld tot een gevestigde en aanbevolen methode voor het uitvoeren van pulmonaal venen isolatie (PVI) in het kader van de behandeling van atriumfibrilleren (AF)[1]. In dit proefschrift wordt de zoektocht naar een balans tussen veiligheid en effectiviteit van cryoballon PVI beschreven en wordt primair gefocust op de mogelijke verbeteringen van het veiligheidsaspect.
In eerste instantie zijn ontwikkelingen en studies met betrekking tot cryoballon PVI voornamelijk gericht geweest op de effectiviteit. Er werd in eerste instantie veel aandacht gericht op het behalen van resultaten die vergelijkbaar waren met de klassieke “gouden standaard” radiofrequente (RF) ablatie. Toentertijd was het veiligheidsaspect een niet vaak genoemd onderwerp in wereldwijd onderzoek. De afgelopen jaren is de focus verlegd. Na de introductie van de tweede generatie cryoballon en nadat de non-inferioriteit ten opzichte van RF ablatie bewezen werd kwam het veiligheidsaspect meer voor het voetlicht. Gedurende de jaren waarin het onderzoek uit dit proefschrift uitgevoerd is, was er een flinke stijging waar te nemen in het aantal studies dat het veiligheidsaspect behandelde.
In zowel RF als cryoballon PVI zijn er verscheidene veiligheidsaspecten om rekening mee te houden. De belangrijkste complicaties van beide methoden waren historisch gezien pulmonaal venen (PV) stenosis, thrombusvorming en (stille) cerebrovasculaire accidenten, tamponade en schade aan omliggende weefsels. Om schade aan omliggende weefsels te voorkomen is er een verscheidenheid aan veiligheidsmaatregelen beschikbaar. Het veiligheidsprofiel van de procedure kan verbeterd worden door belangrijke structuren te monitoren, bijvoorbeeld door het meten van compound motor actie potentialen en oesophagus temperatuur. Het feit dat deze voorzorgsmaatregelen beschikbaar zijn betekent echter niet dat ze alom gebruikt worden. Er is behoefte aan conclusieve studies om deze extra voorzorgsmaatregelen als standaard te integreren in reguliere ablatie procedures. Het beperken van de toegediende RF of cryo energie met behoud van de effectiviteit is een focus van momenteel lopend onderzoek[2].(**Hoofdstuk 2**)

Dosering
Het doseren van cryo energie is een belangrijk focus geworden in pogingen om extra-cardiale schade te verminderen zonder de effectiviteit van de behandeling te beïnvloeden. Historisch gezien zijn meerdere applicaties van 4 minuten, inclusief bonus applicatie na isolatie, de standaarddosering geweest voor cryoballon PVI met de eerste generatie cryoballon[3]. Het gebruik van een enkele alsook kortere applicaties is onderzocht, net als het afzien van bonus applicaties na succesvolle isolatie[4–8]. Protocollen waarin kortere applicatietijden gebruikt worden hebben veelbelovende resultaten laten zien[4,5,9]. Dit waren echter voornamelijk retrospectieve studies en zodoende zijn de optimale cryoballon applicatietijd en dosering strategie nog steeds onderwerp van discussie.

De 123-studie was de eerste gerandomiseerde studie waarin een vergelijking tussen standaard en nieuwe dosering strategieën gemaakt werd. Deze studie liet zien dat er geen (acuut) verschil was wanneer de applicatieduur verkort werd ten opzichte van de historische standaarden, tot applicatie tijden van gemiddelde duur. Kortere applicatietijden hadden een significant negatief effect op het acute succes van de linker maar niet van de rechter PVs. Bovendien resulteerde de verkorting van de

applicatieduur tot korter dan twee minuten in een vermindering van nervus phrenicus letsel. (**Hoofdstuk 3**).

Hoewel er een licht negatief effect op het lange termijn succes waar te nemen was, was er geen bewijs voor inferioriteit voor deze kortere applicatieduur. Voor de rechter bovenste PV geldt dat kortere cryoballon applicaties (<2 minuten) geen effect hadden op de reconductie terwijl er minder nervus phrenicus letsel optrad. (**Hoofdstuk 3 en 4**)

Monitoring
Om de operateur te alarmeren bij dreigende extra-cardiale schade kan er gebruik gemaakt worden van monitoring van kwetsbare weefsels. Op deze manier wordt de operateur in staat gesteld om tijdig de applicatie te onderbreken en op die manier complicaties te voorkomen. Het monitoren van de oesophagus temperatuur kan bijvoorbeeld gebruikt worden om schade aan de oesophagus en de nervus vagus te voorkomen.

Het gebruik van oesophagus temperatuur monitoring tijdens cryoballon PVI zorgt voor een significante vermindering in temperatuur gerelateerde oesophagus laesies. Om oesophagus letsel te voorkomen wordt aangeraden om applicaties te onderbreken bij een temperatuur van 15°C[10]. In **hoofdstuk 5** laten we zien dat lage oesophagus temperaturen zeer regelmatig voorkomen in de reguliere klinische praktijk. In een kwart van de patiënten werden oesophagus temperaturen onder de 20°C gemeten, in de helft daarvan daalde de temperatuur zelfs tot onder de 16°C. Zonder oesophagus temperatuur monitoring zouden deze lage temperaturen onopgemerkt zijn gebleven. Oesophagus schade en schade aan de nervus vagus zorgen voor symptomen die door patiënten niet altijd aan cardiale procedures gerelateerd worden. Zodoende is het zeer wel mogelijk dat deze schade onder gerapporteerd blijft.

Als surrogaat voor het meten van de oesophagus temperatuur wordt er vaak gebruik gemaakt van de ballon temperatuur. De resultaten in **hoofdstuk 5** laten echter zien dat er geen klinisch significante correlatie te vinden is tussen de minimale ballon temperatuur en de laagst gemeten oesophagus temperatuur. Dit is conform eerdere studies naar dit onderwerp[10,11].

Voorspellers
Naast doseren en monitoren is beeldvorming ook een belangrijk instrument om PVI procedures te ondersteunen. Beeldvorming kan gebruikt worden voor het aanmerken van patiënten die tot een risicogroep behoren. Door dit voorafgaand aan de procedure te doen kunnen er in deze groep extra voorzorgsmaatregelen getroffen worden. De afstand van oesophagus tot PV op computed tomography (CT) beelden is een dergelijke voorspeller van verhoogd risico. Een afkapwaarde van 19mm kan gebruikt worden om lage oesophagus temperaturen te voorspellen met een sensitiviteit van 96.2% en een specificiteit van 37.8%. In elke patiënt was er minimaal 1 PV met een oesophagus tot PV afstand van <19mm. Daarom wordt aangeraden om, om oesophagus gerelateerde complicaties te voorkomen, monitoring van oesophagus temperatuur reguliere klinische praktijk te maken. (**Hoofdstuk 5**)

In het kader van ondersteuning van PVI procedures middels beeldvormende technieken heeft 3D CT een aantal voordelen ten opzichte van directe röntgen

doorlichting. Doordat de 3D CT een 3D beeld voor navigatie creëert, wordt het manoeuvreren en plaatsen van de cryoballon een stuk gemakkelijker. (**Hoofdstuk 6**)

Ondanks de kleine populatie toonde onze studie aan dat er potentieel minder stralingsdosis en blootstelling aan contrastvloeistof gedurende de cryoballon PVI procedure is wanneer er gebruik wordt gemaakt van 3D CT. Verdere winst op het gebied van stralingsdosis is te verwachten wanneer in plaats van 3D CT gebruik gemaakt zou worden van 3D magnetic resonance imaging (MRI).

Pre-procedurele CT scans geven gedetailleerde anatomische informatie welke gebruikt kan worden zowel voorafgaand aan als tijdens de procedure. Deze pre-procedurele CT scans kunnen echter ook “bijvangst” met zicht meebrengen in de vorm van toevalsbevindingen van potentiële pathologieën. In zowel de PVI als de percutane aortaklepvervanging populatie komen deze toevalsbevindingen veelvuldig voor[12–23]. De resultaten in **hoofdstuk 7** onderschrijven deze eerdere observaties. Verder draagt hoofdstuk 7 bij aan de huidige discussie omtrent de voordelige en nadelige effecten van het doen van toevalsbevindingen. Een vroege opsporing van extracardiale afwijkingen kan potentieel een snelle en vroege behandeling mogelijk maken. Tegelijkertijd resulteren toevalsbevindingen in extra zorgkosten en daarnaast voor de patiënt ook in hogere stralingsbelasting en mogelijk in angst. Op basis van de resultaten van hoofdstuk 7 kan er bij de voorlichting van patiënten vermeld worden dat, ondanks dat de kans op een toevalsbevinding aanwezig is, er slechts een klein percentage is waarbij ook daadwerkelijk een behandeling noodzakelijk is. Hiermee kan mogelijk de angst bij patiënten verminderd worden.

Conclusie en toekomstperspectieven
Zowel effectiviteit, bepaald door elektrische isolatie, als veiligheid, bepaald door energie dispersie, zijn een resultante van verscheidene factoren. Met behulp van dosering en monitoring strategieën wordt er gepoogd deze factoren onder controle te krijgen. De factoren die hierin met elkaar interacteren zijn echter zo talrijk dat er niet één unieke set van waarden gebruikt kan worden als leidraad voor cryoballon PVI in het algemeen.

Alle dosering en monitoring parameters die op dit moment beschikbaar zijn, zijn helaas nog steeds surrogaat parameters voor het bepalen van de effectiviteit en veiligheid van de procedure. De transmuraliteit van de ablatie energie en het creëren van duurzame (permanente) laesies zijn hierin namelijk de belangrijkste factoren. Om isolatie te bereiken moet de ablatie energie door de atriumwand heen de buitenwand van het atrium (epicard) bereiken en om complicaties te voorkomen moet voorkomen worden dat de energie zich verder verspreidt tot buiten het hart. Daarom zou de grootste focus momenteel moeten liggen op het overstappen van surrogaat parameters naar directe en real-time registratie van laesie vorming. Door middel van directe en real-time metingen zou de operateur directe feedback kunnen krijgen over (cryo)laesie vorming en het optreden van eventuele schade aan omliggende weefsels. Real-time registratie van deze cruciale parameter zou niet alleen een PV of een patiënt specifieke aanpak maar zelfs een applicatie specifieke aanpak mogelijk maken. Met betrekking tot dosering is een eerste veelbelovende stap in de richting van relatief directe registratie gezet door het aanpassen van de applicatietijd aan de tijd tot isolatie (TTI) van de PV. Met behulp van TTI kan patiënt- en PV-specifiek

geregistreerd worden. Het brengt echter nog steeds de transmuraliteit zelf niet in beeld en het geeft geen informatie over de omliggende weefsels.

De ontwikkeling van de derde en vierde generatie cryoballonnen was voornamelijk op directe registratie van PV potentialen en TTI gericht. Helaas kan de TTI nog steeds niet in elke PV gemeten worden. De voornaamste reden hiervoor is dat de Achieve katheter niet alleen gebruikt wordt voor mapping maar ook als voerdraad om de ballon in de gewenste positie te stabiliseren. Onderdeel hiervan is dat de Achieve katheter opgevoerd wordt in de PV waardoor de PV potentialen niet meer te registreren zijn. Het design van de Achieve katheter zou aangepast kunnen worden om dit probleem op te lossen. Door de introductie van een voerdraad die zich onafhankelijk van de elektrodes kan bewegen kunnen PV potentialen proximaal gemeten worden terwijl de voerdraad distaal voor stabilisatie zorgt (Figuur 1).

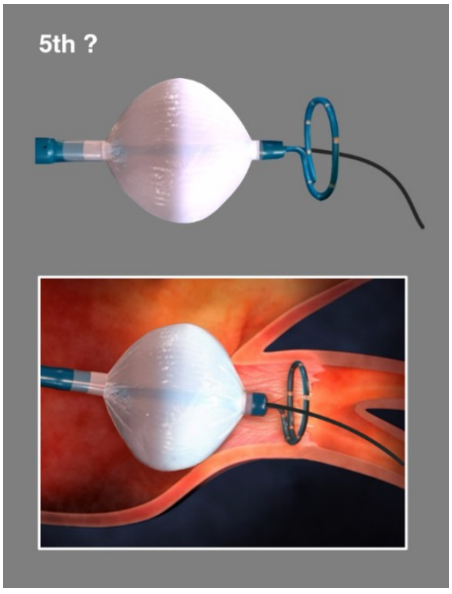

Figure 1 Mogelijk design van de volgende generatie cryoballon. Door de introductie van een voerdraad (zwart in dit figuur) die zich onafhankelijk van de elektrodes kan bewegen kunnen PV potentialen proximaal gemeten worden terwijl de voerdraad distaal voor stabilisatie zorgt (onderste vak). (Figuur op basis van door Medtronic Inc. verstrekte figuren)

De voornaamste kansen voor directere registratie van transmuraliteit en de mate waarin omliggende weefsels bereikt worden liggen bij real-time beeldvorming. Real-time visualisatie van verandering in weefsel gedurende ablatie middels MRI heeft al veelbelovende resultaten laten zien in studies met honden[24]. Wanneer weefsel bevriest, verliest het zijn MRI signaal. Op deze manier kon de vries zone, wat een directe meting is van effectieve bevriezing en ijsformatie in zowel cardiale als niet cardiale structuren, succesvol real-time in beeld gebracht.

De cryoballon heeft een snelle introductie in de klinische praktijk gekend, voornamelijk vanwege de hoge effectiviteit en de laagdrempeligheid van het uitvoeren van de procedure. Pogingen om de procedure te optimaliseren hebben zich, op de introductie van de nieuwe ballonnen na, voornamelijk gericht op het verkrijgen van empirisch bewijs. Dit is gedaan door het trial-and-error principe toe te passen op arbitrair gekozen doseringen qua applicatie duur. Zodoende zou het interessant zijn om een stap terug te doen naar de basis en meer onderzoek te doen naar de thermodynamische eigenschappen van cryoablatie. Recent is aangetoond dat de

effectiviteit van ablatie afhankelijk is van variaties in de onttrokken koude flux25. Ondanks de veelbelovende resultaten van deze studie is het uitdagend gebleken, ook in onze eigen pogingen, om een betrouwbaar model in lab opstelling te creëren (Figuur 2-4). Zelfs wanneer er gebruik wordt gemaakt van een open doos opstelling zijn er nog steeds vele factoren van invloed. Hierdoor is het creëren van een model en het genereren van reproduceerbare resultaten erg uitdagend. Het zou hoogst interessant zijn om een studie uit te voeren naar ijsformatie en koude propagatie waarin technische en klinische experts de handen ineenslaan.

Samenvattend zijn voorspellers waarmee veiligheid vergroot kan worden zijn nog niet zo uitgebreid bestudeerd als voorspellers voor hogere effectiviteit. Bovendien is het veiligheidsaspect voornamelijk in klinische setting bestudeerd. Er is weinig tot niets bekend over het biologische effect van cryo energie terwijl overmatige energieafgifte de cruciale reden is van de voornaamste complicaties van cryoballon PVI. Beter begrip van thermisch gedrag en biofysische parameters die de ijsformatie beïnvloeden is de sleutel naar verbeteringen in het veiligheidsaspect van cryoballon PVI. Het zou ons in staat stellen om modellen te creëren waarmee gedifferentieerde protocolanalyses uitgevoerd kunnen worden. Hiermee zou voorspeld kunnen worden hoe we het optimale effect van cryoballon PVI kunnen bereiken en welke biofysische parameters we gedurende de procedure kunnen gebruiken.

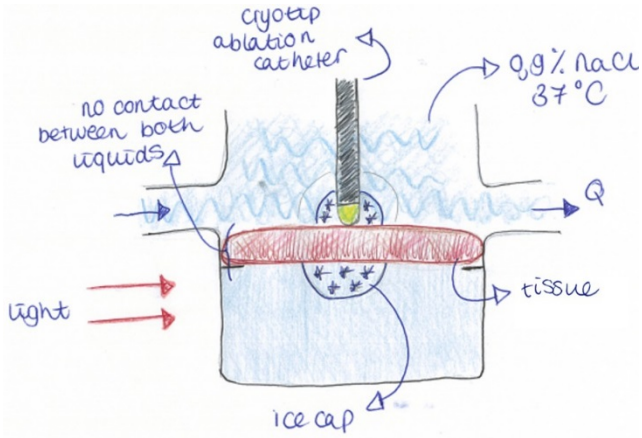

Figure 2 Schematische weergave van het model wat gebruikt is voor de lab opstelling op de Universiteit Twente. Het atrium, de atriumwand en de omliggende weefsels zijn gemodelleerd middels twee 0.9% NaCl oplossingen van 37˚C met een plakje weefsel er tussenin. De omgeving van het atrium werd gerepresenteerd door een vloeistof zonder flow, de atriumholte werd gerepresenteerd door dezelfde vloeistof mèt flow Q. Het weefsel werd tegen de wand van het model geklemd om ervoor te zorgen dat er geen contact was tussen de twee vloeistoffen. Met een cryotip ablatiecatheter werden er twee cycli van ablatie uitgevoerd. De interne en externe ijskap die door de ablatie ontstonden in het gemodelleerde “atrium” en in de “omgeving” werd visueel gemeten met behulp van een raster (nadat licht intensiteit, echo en temperatuur camera metingen niet geschikt bleken).

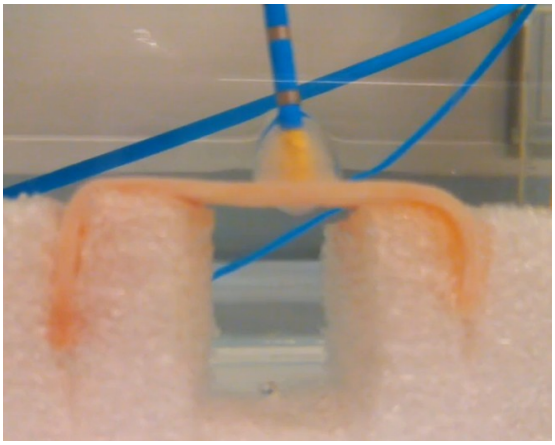

Figure 3 Gedetailleerde weergave van een van de modellen, hierin is het raster nog niet geplaatst. Om de katheter heen is een grote “interne” ijskap te onderscheiden, net als een kleinere “externe” ijskap aan de onderkant van het weefsel.

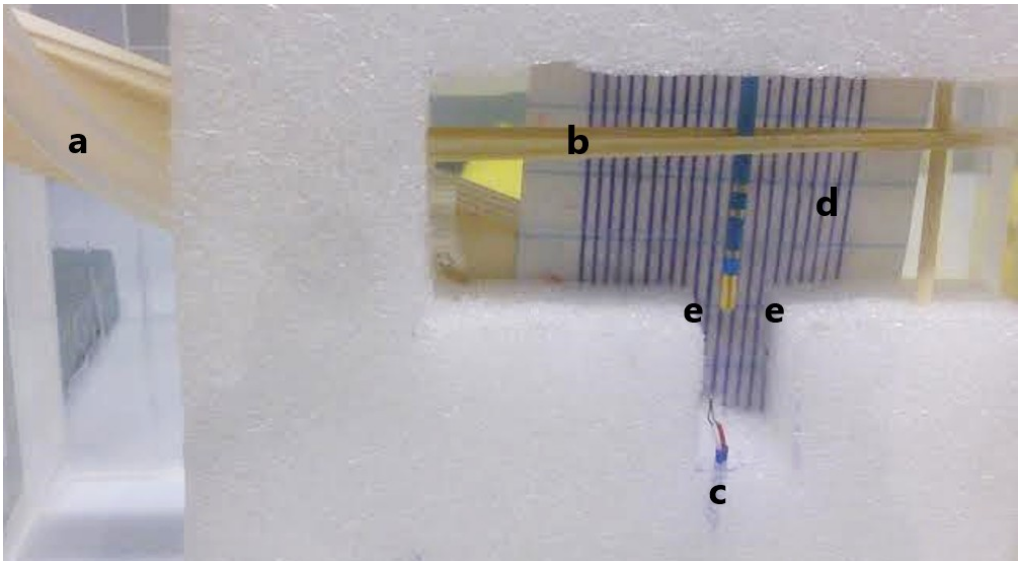

Figure 4 Lab opstelling zoals gebruikt met a. de buis waardoor de pulsatiele flow van 37 ˚C stroomde, b. een houten frame, om interferentie met geleidingseigenschappen te voorkomen, om de katheter in te fixeren, c. een temperatuur sensor, die zich in de “omgeving” van het hart bevindt, d. het raster waarop de afmeting van de ijskap diameters gemeten werd en e. de wanden waartegen het weefsel werd geklemd (geen weefsel aanwezig in dit figuur).

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Thoraxchirurgie

Innovations in cardio-thoracic surgery:
predicting and optimising outcome with state of the heart technology

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 donderdag 29 oktober 2020 om 16:45 uur

door

Frank Ruben Halfwerk
geboren op 26 september 1989
te Hardenberg, Nederland

Promotoren: Prof. dr. J.G. Grandjean
prof. dr. ir. H.F.J.M. Koopman

Samenvatting
Cardio-thoracale chirurgie of hartchirurgie focust zich op de chirurgische behandeling van hart, longen, mediastinum, grote intra thoracale bloedvaten, het diafragma en de thoraxwand. Veel operatietechnieken stammen nog uit de periode 1950 tot 1980 en worden nog steeds veel gebruikt. Desalniettemin zijn lange termijn uitkomsten van hartchirurgie ongeëvenaard t.o.v. cardiologische behandelingen. Een groot ervaren nadeel van hartchirurgie is de omvang van de ingreep. Daardoor daalt het aantal ingrepen en wordt er voornamelijk geld en aandacht aan andere disciplines zoals de interventiecardiologie geïnvesteerd.

Om de uitkomsten van hartchirurgie te verbeteren en te voorkomen dat hartchirurgie een tweederangs behandeling wordt zijn diverse thema's geïdentificeerd. Dit proefschrift richt zich op minimaal invasieve chirurgie, technologische innovaties en een multidisciplinaire aanpak om de uitkomsten voor patiënten te verbeteren. De hypothese is dat hartchirurgie, met slechts één interventie, een goede behandeloptie voor patiënten blijft als deze thema's worden toegepast in de klinische praktijk.

DEEL I: Minimaal invasieve hartchirurgie

Verminderen van de effecten van de hart-long machine
Een hart-long machine (cardiopulmonaire bypass, CPB) neemt de pompfunctie van het hart en gasuitwisseling van de longen over tijdens open hartchirurgie. Grote nadelen van CPB zijn een systemische ontstekingsreactie, acute nierschade en hersenberoertes. Minimaal-invasieve extracorporale circulatie (MiECC) vermindert de systemische ontstekingsreactie door het bloed-lucht contact te verminderen, het circulerend volume te verkleinen en cel-interacties tussen bloedcellen en contactoppervlakken te voorkomen.

In **Hoofdstuk 2** zijn de effecten van CPB verminderd door gebruik te maken van MiECC voor geïsoleerde aortaklep vervangingen. In een gerandomiseerde studie zijn 125 patiënten geloot in de MiECC groep of een geavanceerde conventionele extracorporale circulatie (AdECC). Patiënten in de MiECC groep hadden significant minder bloedverlies dan de AdECC groep (230 vs. 288 mL), maar dit heeft geen klinische impact. Er was geen verschil in het aantal bloedtransfusies of andere klinische uitkomsten.

Sommige hartcentra geven de voorkeur aan een conventioneel systeem door vermeende veiligheidsrisico's bij het gebruik van MiECC en de lange trainingsduur van OK-personeel. Een AdECC systeem met inerte contactoppervlakken, een centrifugaal pomp en arteriële filters kan dus een goed alternatief zijn voor deze ziekenhuizen.

Verbeteren van intra-operatieve metingen tijdens coronaire bypass chirurgie
De kransslagaderen voorzien het hart van zuurstof en voedingsstoffen. Vernauwingen (stenosen) kunnen leiden tot pijn op de borst of zelfs een hartinfarct. Om symptomen, kwaliteit van leven en overleving te verbeteren kan een dotterbehandeling of omleidingsoperatie (coronaire bypass grafting, CABG) worden uitgevoerd. Helaas is de mate van stenose peroperatief lastig in te schatten, wat leidt tot suboptimale lange termijn resultaten van CABG.

Met behulp van Transit Time Flow Metingen (TTFM) kan intra-operatief de bloedstroom door de omleiding worden bepaald. Klinisch-relevante afkapwaarden van TTFM verschillen erg tussen studies en zijn daarom nog niet in behandelrichtlijnen vastgelegd. In **Hoofdstuk 3** worden peroperatieve inschattingen van coronaire stenosen gecombineerd met intra-operatieve TTFM in 50 CABG patiënten, zonder gebruik te maken van een hart-long machine (off-pump CABG).

Het doel van de studie is om de impact van stenose in de linker voorste dalende kransslagader (LAD) op competitieve flow in de graft (linker borstwand slagader) te bepalen. Competitieve flow is verminderde bloedstroom door de graft door te veel resterende flow in de kransslagader. In deze studie is tevens een nieuwe parameter ontwikkeld: de competitieve flow index (CFI) als verhouding tussen de gemiddelde graft flow (MGF) met de kransslagader (tijdelijk) dicht en open.

Door de LAD tijdelijk dicht te maken steeg de MGF van 20 mL/min naar 30 mL/min. Deze stijging was ook aanwezig toen de mate van stenose in drie groepen werd ingedeeld. Bij 26 patiënten (52%) was de MGF lager dan de klinisch relevante afkapwaarden uit de literatuur. De MGF steeg bij 16 van deze patiënten naar een acceptabele waarde bij het tijdelijk afsluiten van de LAD. Bij patiënten met een ernstige vernauwing (> 70% stenose) was de CFI veel lager dan patiënten met een milde vernauwing (< 50% stenose).

Routinematig gebruik van de CFI kan helpen om competitieve flow in kaart te brengen tijdens de omleidingsoperatie als TTFM geen uitsluitsel biedt. Er is nog meer onderzoek nodig om de rol van CFI en het tijdelijk afsluiten van de kransslagader op uitkomsten na CABG vast te stellen.

De polsslagader: geschikt voor eenmalig gebruik of hergebruik?
Hartkatheterisatie wordt gebruikt om stenosen in de kransslagaders in kaart te brengen. Als toegangsweg wordt voornamelijk de polsslagader (a. radialis) gebruikt. Tegelijkertijd adviseren Europese richtlijnen de a. radialis als CABG graft. Door hartkatheterisatie loopt de a. radialis schade op en kan daardoor niet goed meer open blijven.

Het is onbekend (1) hoe vaak de a. radialis zowel gebruikt wordt voor hartkatheterisatie als CABG, (2) hoe cardiologen in de praktijk omgaan met dit dilemma en (3) of cardiologen op de hoogte zijn van de Europese richtlijnen uit 2018. In **hoofdstuk 4** wordt dit onderzocht middels een retrospectief data-onderzoek en semigestructureerde interviews onder 50 Nederlandse cardiologen.

Van de 3100 CABG patiënten was minimaal één van de twee aa. radiales tussen 2008 – 2015 in 0.3% van de patiënten reeds gebruikt voor hartkatheterisatie. Dit percentage steeg tot 2.4% tussen 2016-2018. Bij 9 patiënten werd de a. radialis dubbel gebruikt, waarvan één patiënt een her operatie nodig had vanwege graft disfunctie.

Alle 50 cardiologen gaven aan bekend te zijn met de richtlijnen. Maar liefst 56% was niet bekend met het klinische dilemma, waar 18% aangaf dat dit überhaupt geen dilemma is. Interventiecardiologen hadden vaker (64%) een voorkeur voor de linker a.

radialis indien de rechter a. radialis onbruikbaar was, dan niet-interventiecardiologen (23%).

Slechts 10% van de cardiologen gaf aan dit dilemma eerder te hebben meegemaakt. Na de interviews zei 36% dat ze de toegangsweg mogelijk gaan aanpassen om de linker a. radialis te bewaren voor een eventuele CABG. Als beslishulp is daarom een stroomdiagram met adviezen gemaakt voor op de hartkatheterisatiekamer.

DEEL II: Technische innovaties in de cardio-thoracale chirurgie

Superkritische CO2-behandeling van het hartzakje voor toepassingen in de cardio-thoracale chirurgie
In de cardio-thoracale chirurgie worden veel biomaterialen gebruikt met goede korte termijn resultaten. Helaas verkalken deze materialen, er ontstaat littekenweefsel of het biomateriaal wordt afgebroken zoals bij kunsthartkleppen.

Het doel van **hoofdstuk 5** is om het hartzakje van varkens en runderen te ontdoen van dierlijke cellen met superkritisch CO2 en de goede eigenschappen te behouden voor toepassingen in de cardio-thoracale chirurgie. Verse en met glutaaraldehyde-behandelde hartzakjes zijn met elkaar vergeleken op mechanische en structuur eigenschappen.

Hartzakjes behandeld met superkritisch CO2 behouden hun treksterkte, terwijl de treksterkte van hartzakjes behandeld met glutaaraldehyde juist steeg. Hetzelfde geldt voor de structuur eigenschappen van het hartzakje, waar glutaaraldehyde de extracellulaire matrix beschadigde en deze bij superkritisch CO2 intact bleef.

De initiële eigenschappen van het hartzakje zijn zeer bruikbaar voor toepassingen in de cardio-thoracale chirurgie. Het behoud van deze eigenschappen na een superkritische CO2 behandeling is daarom veelbelovend.

Verbeteren van de pomp functie van het hart met slimme materialen
Bij hartfalen is het hart niet meer in staat voldoende bloed rond te pompen. Dit leidt tot klachten van benauwdheid bij inspanning. Helaas is er geen genezing van hartfalen mogelijk. De 5-jaarssterfte ligt op 50% en is daarmee hoger dan vele soorten kanker.

Recent zijn in het lab smart memory alloys (SMA) in de context van hartfalen onderzocht.

In **hoofdstuk 6** wordt onderzocht of de pompfunctie van het hart met 5% kan worden verbeterd in een ventilatieballonmodel door diverse SMA configuraties en met pulsbreedtemodulatie. De SMA-windingen zijn zowel als spiraal, band, kruislings en schuin aangebracht. Een 380 µm SMA draad in een spiraalvorm met een duty cycle van 80% en een frequentie van 50/min gaf de hoogste volume verplaatsing van 6.2 mL. Hiermee werd een pompfunctie van 3.5% behaald.

Het huidige ontwerp geeft nog geen klinisch relevante verbetering van benauwdheidssymptomen. Toekomstig onderzoek moet de spiraalvormige ontwerpen om het hart gaan testen in dynamische modellen of op een ex vivo varkens hart.

DEEL III: Multidisciplinaire aanpak ter verbetering van hartchirurgie

Bewegen is herstellen!
Hoofdstuk 7 beschrijft een prospectieve studie waarbij ziekenhuismobilisatie na hartchirurgie wordt verbeterd met een mobilisatieposter. Patiënten krijgen hierdoor meer regie over hun eigen herstel en zijn gevraagd om feedback op de poster te geven. Activiteiten zoals in bed liggen, zitten, lopen naar de eigen badkamer, lopen op de gang, fietsen op een home trainer en traplopen zijn onderzocht in een samengestelde maat van de American College of Sports Medicine (ACSM) en een zelf ontworpen Thoraxcentrum Twente (TCT) score.

De ACSM functionele score toonde dagelijkse ontwikkeling van mobilisatie op de verpleegafdeling na hartchirurgie. De interventieposter gaf hier geen verbetering op. De TCT scores zitten, lopen naar de badkamer, lopen op de gang en fietsen verbeterden wel met de interventieposter. Er was geen verschil in ziekenhuisduur of overleving. Verrassend genoeg hadden mannen hogere ACSM-scores dan vrouwen. Patiënten gaven aan de poster helder, motiverend en niet opdringerig te vinden. Familieleden waren met de poster meer betrokken bij het herstel van patiënten.

Bovenstaande activiteiten kunnen nog sneller ontwikkelen als er patiënt- en dagspecifieke oefeningen worden aangeboden middels persuasieve strategieën. Het verschil tussen mannen en vrouwen moet worden onderzocht met objectieve meetmethoden zoals met draagbare technologie.

Heel kundig handelen vóór patiëntenzorg
Dit proefschrift eindigt daar waar (technische) geneeskunde studenten hun klinische carrière starten.

In **hoofdstuk 8** wordt een chirurgisch vaardigheidscurriculum voor masterstudenten Technische Geneeskunde ontworpen en geëvalueerd op basis van bekwaamheid in een gesimuleerde beroepspraktijk. Leeruitkomsten als kennis en vaardigheid zijn onderzocht alsook reacties van studenten tijdens de klinische stages.

In het chirurgisch vaardigheidsonderwijs staat de patiëntroute tijdens een chirurgische opname nu centraal. Het vak richt zich op anatomische en fysiologische kennis, technische vaardigheden en professionele vaardigheden zoals besluitvoering en leiderschap. De beoordelaars van het praktijkexamen werden getraind om subjectieve beoordelingen te voorkomen.

Tijdens de klinische stages hanteerden studenten steriel instrumentarium, gebruikten ze steriele technieken op en rond de operatiekamer en voerden ze hechttechnieken uit. De meerderheid van studenten voelde zich zelfverzekerd tijdens (het bijwonen van) operaties en gaven aan een professionele houding aan te kunnen nemen.

Op basis van dit onderzoek bevelen we aan dat een chirurgisch vaardigheidscurriculum op basis van bekwaamheid in een gesimuleerde beroepspraktijk standaard zou moeten zijn voordat studenten de patiëntenzorg in gaan.

Algemene conclusie en aanbevelingen
Minimaal invasieve hartchirurgie kan voor grote patiëntengroepen leiden tot betere uitkomsten door het verminderen van de effecten van een hart-long machine. Het combineren van patiëntkarakteristieken en operatietechnieken moet de beslisvorming voor een (minimaal invasieve) hartoperatie, katheter behandeling, of afzien van behandeling nog verder gaan ondersteunen. Technische ontwikkelingen zoals verbeterde biomaterialen voor reconstructieve hartchirurgie en slimme materialen gaan de resultaten van hartchirurgie voor patiënten verder verbeteren.

Veel potentiële nadelen aan off-pump CABG zijn gerelateerd aan het aanleren hiervan. Vaak is off-pump CABG training niet aanwezig voor arts-assistenten of hartchirurgen, richt het zich puur op de handeling zelf of wordt het überhaupt niet gebruikt. Daarom moet een chirurgisch vaardigheidscurriculum op basis van bekwaamheid in een gesimuleerde beroepspraktijk een vereiste zijn voordat technieken in de patiëntenzorg worden toegepast.

Ten laatste zal alleen een multidisciplinaire aanpak met gezamenlijke besluitvoering tussen patiënten (technisch) medisch specialisten, verpleegkundigen, fysiotherapeuten en andere aanverwante beroepen leiden tot betere uitkomsten van hartchirurgie.

PubMed publicaties per vakgroep
Anesthesie

1. For debate: advanced bleeding control potentially saves lives in armed forces and should be considered
Borger van der Burg BLS, Keijzers P, van Dongen T, van Waes OJF, Hoencamp R.

Introduction: Advanced bleeding control options for truncal and junctional haemorrhage including resuscitative endovascular balloon occlusion of the aorta (REBOA) have been used in managing catastrophic bleeding. The primary aim is to report on potential indications for advanced bleeding control in combat casualties during the Dutch deployment in Uruzgan, Afghanistan, between August 2006 and August 2010. The secondary aim is to report on training methods for advanced bleeding control in (para)medical personnel.
Methods: The trauma registry from the Dutch role 2 enhanced medical treatment facility at Tarin Kowt, Uruzgan, Afghanistan, was used to analyse patients who sustained a battle injury with major haemorrhage. Furthermore, a comprehensive search was performed on training (para)medical personnel in advanced bleeding control.
Results: There were 212 possible indications for advanced bleeding control with mortality of 28.8% (61/212). These possible indications consisted of 1.9% (4/212) junctional lower extremity injuries with a 75% (3/4) mortality rate, 59% (125/212) visceral vascular injuries with a mortality rate of 12.5% (26/125). The junctional and visceral injuries (n=129) were all potential indications for advanced bleeding control options, such as REBOA. Further 39.2% (83/212) casualties with central thoracic or neck injuries had a mortality rate of 38.6% (32/83). Based on an Abbreviated Injury Scale chest or abdomen score ≥461 indications for advanced bleeding control were identified. A 24-hour average of 8.8 packets of red blood cells, 4.2 packets of plasma and 1.9 packets of platelets was used to prevent exsanguination. The total out-of-hospital survival rate was 64% (39/61).
Conclusion: Retrospective analysis revealed 212 potential indications for advanced bleeding control with a mortality of 28.8% (61/212). Advanced bleeding control, such as REBOA, might have improved survival in approximately 61 of 212 casualties. Advanced bleeding control could be used as an adjunct to improve outcomes in major truncal or junctional haemorrhage in prehospital, remote settings and implementation should be considered. Vascular access training and REBOA placement for (para)medical military personnel should be explored in future research.

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Impact factor: nvt; nvt

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2. Effect of electroacupuncture on sedation requirements during colonoscopy: a prospective placebo-controlled randomised trial
Eberl S, Monteiro de Olivera N, Bourne D, Streitberger K, Fockens P, Hollmann MW, Preckel B.

Introduction: Propofol provides excellent sedation during colonoscopy. However, its application, namely when used together with an opioid, is associated with

cardiopulmonary depression. Acupuncture is used nowadays for the treatment of pain and anxiety, and also to induce sedation. We hypothesised that electroacupuncture (EA) during colonoscopy would have sedative effects, thereby reducing propofol requirements to achieve an adequate level of sedation.
Method: The study was designed and conducted as a single centre, patient and observer blinded, sham- and placebo-controlled randomised trial. Patients scheduled for elective colonoscopy under deep propofol/alfentanil sedation were randomly assigned to receive unilateral EA, sham-acupuncture (SA) or placebo-acupuncture (PA) at ST36, PC6 and LI4. The primary outcome parameter was the total dosage of propofol. Secondary outcomes included the patients' and endoscopists' satisfaction levels evaluated by questionnaires.
Results: The dosage of propofol required (median [IQR]) was not significantly different between the three groups (EA group 147 µg/kg/min [109-193] vs SA group 141 µg/kg/min [123- 180] vs PA group 141 µg/kg/min [112-182]; P=0.776). There was also no significant difference in alfentanil consumption (P=0.634). Global satisfaction (median [IQR]) among patients (EA group 6.6 [6.0-7.0] vs SA group 6.8 [6.0-7.0] vs PA group 6.5 [6.0-7.0]; P=0.481) and endoscopists (6.0 [5.0-6.0] for all groups; P=0.773) did not significantly differ between the three groups. There was no significant difference in the number of cardiorespiratory events.
Conclusion: For colonoscopy, the applied mode of EA did not show any propofol-sparing sedative effect compared with sham or placebo acupuncture.
Trial registration: The trial is registered in the Netherland's Trial Registry (NTR4325).

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Impact factor: 2.129; Q2

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3. Postoperative Hypotension after Noncardiac Surgery and the Association with Myocardial Injury
Liem VGB, Hoeks SE, Mol K, Potters JW, Grüne F, Stolker RJ, van Lier F.

Background: Intraoperative hypotension has been associated with postoperative morbidity and early mortality. Postoperative hypotension, however, has been less studied. This study examines postoperative hypotension, hypothesizing that both the degree of hypotension severity and longer durations would be associated with myocardial injury.
Methods: This single-center observational cohort was comprised of 1,710 patients aged 60 yr or more undergoing intermediate- to high-risk noncardiac surgery. Frequent sampling of hemodynamic monitoring on a postoperative high-dependency ward during the first 24 h after surgery was recorded. Multiple mean arterial pressure (MAP) absolute thresholds (50 to 75 mmHg) were used to define hypotension characterized by cumulative minutes, duration, area, and time-weighted-average under MAP. Zero time spent under a threshold was used as the reference group. The primary outcome was myocardial injury (a peak high-sensitive troponin T measurement 50 ng/l or greater) during the first 3 postoperative days.
Results: Postoperative hypotension was common, e.g., 2 cumulative hours below a threshold of 60 mmHg occurred in 144 (8%) patients while 4 h less than 75 mmHg occurred in 824 (48%) patients. Patients with myocardial injury had higher prolonged exposures for all characterizations. After adjusting for confounders, postoperative

duration below a threshold of 75 mmHg for more than 635 min was associated with myocardial injury (adjusted odds ratio, 2.68; 95% CI, 1.46 to 5.07, P = 0.002). Comparing multiple thresholds, cumulative durations of 2 to 4 h below a MAP threshold of 60 mmHg (adjusted odds ratio, 3.26; 95% CI, 1.57 to 6.48, P = 0.001) and durations of more than 4 h less than 65 mmHg (adjusted odds ratio, 2.98; 95% CI, 1.78 to 4.98, P < 0.001) and 70 mmHg (adjusted odds ratio, 2.18; 95% CI, 1.37 to 3.51, P < 0.001) were also associated with myocardial injury. Associations remained significant after adjusting for intraoperative hypotension, which independently was not associated with myocardial injury.
Conclusions: In this study, postoperative hypotension was common and was independently associated with myocardial injury.

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Impact factor: 7.067; Q1

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4. Use of the Humeral Head as a Reference Point to Prevent Axillary Nerve Damage during Proximal Fixation of Humeral Fractures: An Anatomical and Radiographic Study
Theeuwes HP, Potters JW, Bessems J, Kerver AJ, Kleinrensink GJ.

Introduction: Treatment of proximal humeral fractures with plate osteosynthesis or intramedullary nail fixation in humeral shaft fractures with a proximal locking bolt carries the risk of iatrogenic injury of the axillary nerve. The purpose of this anatomical study is to define a more reliable safe zone to prevent iatrogenic axillary nerve injury using the humeral head instead of the acromion as a (radiographic) reference point during operative treatment. MATERIALS AND
Methods: Anatomical dissection and labeling of the axillary nerve and branches was performed on 10 specially embalmed human specimens. Standard AP and straight lateral radiographs were made. The distances were measured indirectly from the cranial tip of the humerus to the axillary nerve on radiographs.
Results: The median distance from the cranial tip of the humerus to the axillary nerve was 52 mm. The mean number of axillary nerve branches was 3. The distances from the cranial tip of the humerus to the nerve (branch) varied from 23 to 78 mm. The median distance from the proximal (anterior) branch was 36 mm, to the second branch 47 mm, 54 mm to the third branch and 73 mm to the fourth branch. The axillary nerve moves along with the humerus in cranial and caudal direction when the subacromial space varies.
Conclusion: This study shows that the position of the axillary nerve can be better determent using the cranial tip of the humerus as a reference point instead of the acromion. Furthermore, it is unsafe to place the proximal locking bolts in the zone between 24 mm and 78 mm from the cranial tip of the humerus. The greatest chance to cause a lesion of the main branch of the axillary nerve is in the zone between 48 mm and 58 mm caudal from the tip of the humeral head. HOW TO CITE THIS ARTICLE: Theeuwes HP, Potters JW, Bessems JHJM, et al. Use of the Humeral Head as a Reference Point to Prevent Axillary Nerve Damage during Proximal Fixation of Humeral Fractures: An Anatomical and Radiographic Study. Strategies Trauma Limb Reconstr 2020;15(2):63-68.

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Gemiddelde impact factor: 0.710

Cardiologie

1. External validation of existing prediction models of 30-day mortality after Transcatheter Aortic Valve Implantation (TAVI) in the Netherlands Heart Registration
Al-Farra H, Abu-Hanna A, de Mol B, Ter Burg WJ, Houterman S, Henriques JPS, Ravelli ACJ, NHR THI Registration Committee, includes Stoel M.

Background: Several mortality prediction models (MPM) are used for predicting early (30-day) mortality following transcatheter aortic valve implantation (TAVI). Little is known about their predictive performance in external TAVI populations. We aim to externally validate established MPMs on a large TAVI dataset from the Netherlands Heart Registration (NHR).
Methods: We included data from NHR-patients who underwent TAVI during 2013-2017. We calculated the predicted mortalities per MPM. We assessed the predictive performance by discrimination (Area Under Receiver Operating-characteristic Curve, AU-ROC); the Area Under Precision-Recall Curve, AU-PRC; calibration (using calibration-intercept and calibration-slope); Brier Score and Brier Skill Score. We also assessed the predictive performance among subgroups: tertiles of mortality-risk for non-survivors, gender, and access-route.
Results: We included 6177 TAVI-patients with an observed early-mortality rate of 4.5% (n=280). We applied seven MPMs (STS, EuroSCORE-I, EuroSCORE-II, ACC-TAVI, FRANCE-2, OBSERVANT, and German-AV) on our cohort. The highest AU-ROCs were 0.64 (95%CI 0.61-0.67) for ACC-TAVI and 0.63 (95%CI 0.60-0.67) for FRANCE-2. All MPMs had a very low AU-PRC of </=0.09. ACC-TAVI had the best calibration-intercept and calibration-slope. Brier Score values ranged between 0.043 and 0.063. Brier Skill Score ranged between -0.47 and 0.004. ACC-TAVI and FRANCE-2 predicted high mortality-risk better than other MPMs. ACC-TAVI outperformed other MPMs in different subgroups.
Conclusion: The ACC-TAVI model has relatively the best predictive performance. However, all models have poor predictive performance. Because of the poor discrimination, miscalibration and limited accuracy of the models there is a need to update the existing models or develop new TAVI-specific models for local populations.

Gepubliceerd: Int J Cardiol. 2020;317:25-32.
Impact factor: 3.229; Q2

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2. Dutch cardiology residents and the COVID-19 pandemic: Every little thing counts in a crisis
Berger WR, Baggen V, Vorselaars VMM, van der Heijden AC, van Hout GPJ, Kapel GFL, Woudstra P.

The COVID-19 pandemic has overwhelmed healthcare systems worldwide, and a large part of regular cardiology care came to a quick halt. A Dutch nationwide survey showed that 41% of cardiology residents suspended their training and worked at COVID-19 cohort units for up to 3 months. With tremendous flexibility, on-call schedules were altered and additional training was provided in order for residents to

be directly available where needed most. These unprecedented times have taught them important lessons on crisis management. The momentum is used to incorporate novel tools for patient care. Moreover, their experience of pandemic and crisis management has provided future cardiologists with unique skills. This crisis will not be wasted; however, several challenges have to be overcome in the near future including, but not limited to, a second pandemic wave, a difficult labour market due to an economic recession, and limitations in educational opportunities.

Gepubliceerd: Neth Heart J. 2020;28(12):625-7.
Impact factor: 1.933; Q3

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3. Aspirin with or without Clopidogrel after Transcatheter Aortic-Valve Implantation

Brouwer J, Nijenhuis VJ, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, Frambach P, De Bruyne B, van Houwelingen GK, Van Der Heyden JAS, Toušek P, van der Kley F, Buysschaert I, Schotborgh CE, Ferdinande B, van der Harst P, Roosen J, Peper J, Thielen FWF, Veenstra L, Chan Pin Yin D, Swaans MJ, Rensing B, van 't Hof AWJ, Timmers L, Kelder JC, Stella PR, Baan J, Ten Berg JM.

Background: The effect of single as compared with dual antiplatelet treatment on bleeding and thromboembolic events after transcatheter aortic-valve implantation (TAVI) in patients who do not have an indication for long-term anticoagulation has not been well studied.
Methods: In a randomized, controlled trial, we assigned a subgroup of patients who were undergoing TAVI and did not have an indication for long-term anticoagulation, in a 1:1 ratio, to receive aspirin alone or aspirin plus clopidogrel for 3 months. The two primary outcomes were all bleeding (including minor, major, and life-threatening or disabling bleeding) and non-procedure-related bleeding over a period of 12 months. Most bleeding at the TAVI puncture site was counted as non-procedure-related. The two secondary outcomes were a composite of death from cardiovascular causes, non-procedure-related bleeding, stroke, or myocardial infarction (secondary composite 1) and a composite of death from cardiovascular causes, ischemic stroke, or myocardial infarction (secondary composite 2) at 1 year, with both outcomes tested sequentially for noninferiority (noninferiority margin, 7.5 percentage points) and superiority.
Results: A total of 331 patients were assigned to receive aspirin alone and 334 were assigned to receive aspirin plus clopidogrel. A bleeding event occurred in 50 patients (15.1%) receiving aspirin alone and in 89 (26.6%) receiving aspirin plus clopidogrel (risk ratio, 0.57; 95% confidence interval [CI], 0.42 to 0.77; P = 0.001). Non-procedure-related bleeding occurred in 50 patients (15.1%) and 83 patients (24.9%), respectively (risk ratio, 0.61; 95% CI, 0.44 to 0.83; P = 0.005). A secondary composite 1 event occurred in 76 patients (23.0%) receiving aspirin alone and in 104 (31.1%) receiving aspirin plus clopidogrel (difference, -8.2 percentage points; 95% CI for noninferiority, -14.9 to -1.5; P<0.001; risk ratio, 0.74; 95% CI for superiority, 0.57 to 0.95; P = 0.04). A secondary composite 2 event occurred in 32 patients (9.7%) and 33 patients (9.9%), respectively (difference, -0.2 percentage points; 95% CI for noninferiority, -4.7 to 4.3; P = 0.004; risk ratio, 0.98; 95% CI for superiority, 0.62 to 1.55; P = 0.93). A total of 44 patients (13.3%) and 32 (9.6%), respectively, received oral anticoagulation during the trial.

Conclusions: Among patients undergoing TAVI who did not have an indication for oral anticoagulation, the incidence of bleeding and the composite of bleeding or thromboembolic events at 1 year were significantly less frequent with aspirin than with aspirin plus clopidogrel administered for 3 months. (Funded by the Netherlands Organization for Health Research and Development; POPular TAVI EU Clinical Trials Register number, 2013-003125-28; ClinicalTrials.gov number, NCT02247128.).

Gepubliceerd: N Engl J Med. 2020;383(15):1447-57.
Impact factor: 74.699; Q1

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4. Thin Composite-Wire-Strut Zotarolimus-Eluting Stents Versus Ultrathin-Strut Sirolimus-Eluting Stents in BIONYX at 2 Years
Buiten RA, Ploumen EH, Zocca P, Doggen CJM, Jessurun GAJ, Schotborgh CE, Roguin A, Danse PW, Benit E, Aminian A, van Houwelingen KG, Schramm AR, Stoel MG, Somi S, Hartmann M, Linssen GCM, von Birgelen C.

Objectives: The aim of this study was to assess 2-year safety and efficacy of the current-generation thin composite-wire-strut durable-polymer Resolute Onyx zotarolimus-eluting stent (ZES), compared with the ultrathin-strut biodegradable-polymer Orsiro sirolimus-eluting stent (SES) in all-comers and a pre-specified small-vessel subgroup analysis.
Background: The Resolute Onyx ZES is widely used in clinical practice, but no follow-up data beyond 1 year have been published. The randomized BIONYX (Bioresorbable Polymer-Coated Orsiro Versus Durable Polymer-Coated Resolute Onyx Stents) trial (NCT02508714) established the noninferiority of ZES versus SES regarding target vessel failure (TVF) rates.
Methods: A total of 2,488 all-comer patients were treated at 7 coronary intervention centers in Belgium, Israel, and the Netherlands. The main endpoint, TVF, was a composite of safety (cardiac death or target vessel-related myocardial infarction) and efficacy (clinically indicated target vessel revascularization). Two-year follow-up data were analyzed using Kaplan-Meier methods.
Results: Two-year follow-up data were available for 2,460 of 2,488 patients (98.9%). TVF occurred in 93 of 1,243 patients (7.6%) assigned to ZES versus 87 of 1,245 patients (7.1%) assigned to SES (log-rank p = 0.66). There was no significant between-stent difference in individual components of this endpoint. The incidence of definite-or-probable stent thrombosis was low for both treatment arms (0.4% vs. 1.1%; log-rank p = 0.057). In patients stented in small vessels, there was no between-stent difference (TVF 8.2% vs. 8.7% [log-rank p = 0.75], target lesion revascularization 4.0% vs. 4.4% [log-rank p = 0.77]).
Conclusions: At 2-year follow-up, the novel thin composite-wire-strut durable-polymer Resolute Onyx ZES showed in all-comers similar safety and efficacy compared with the ultrathin cobalt-chromium-strut biodegradable-polymer Orsiro SES. The analysis of patients who were treated in small vessels also suggested no advantage for either stent.

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Impact factor: 8.432; Q1

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5. Three contemporary thin-strut drug-eluting stents implanted in severely calcified coronary lesions of participants in a randomized all-comers trial
Buiten RA, Ploumen EH, Zocca P, Doggen CJM, van Houwelingen KG, Danse PW, Schotborgh CE, Stoel MG, Scholte M, Linssen GCM, de Man F, von Birgelen C.

Objective: The objective was to assess the 2-year clinical performance of three drug-eluting stents in all-comer patients with severely calcified coronary lesions.
Background: Severe lesion calcification increases cardiovascular event risk after coronary stenting, but there is a lack of data on the clinical outcome of all-comers with severely calcified lesions who were treated with more recently introduced drug-eluting stents.
Methods: The BIO-RESORT trial (clinicaltrials.gov: NCT01674803) randomly assigned 3,514 all-comer patients to biodegradable polymer Synergy everolimus-eluting stents (EES) or Orsiro sirolimus-eluting stents (SES), versus durable polymer Resolute Integrity zotarolimus-eluting stents (ZES). In a post hoc analysis, we assessed 783 patients (22.3%) with at least one severely calcified target lesion.
Results: At 2-year follow-up (available in 99% of patients), the main composite endpoint target vessel failure occurred in 19/252 (7.6%) of the EES and in 33/265 (12.6%) of the ZES-treated patients (p = .07). Target vessel failure occurred in 24/266 (9.1%) of the SES-treated patients (vs. ZES: p = .21). There was a difference in target vessel revascularization, which was required in EES in 6/252 (2.4%) patients and in ZES in 20/265 (7.7%) patients (p = .01); the target vessel revascularization rate in SES was 9/266 (3.4%, vs. ZES: p = .04). Multivariate analysis showed that implantation of EES, but not SES, was independently associated with lower target vessel revascularization rates than in ZES.
Conclusions: In BIO-RESORT participants with severely calcified target lesions, treatment with EES was associated with a lower 2-year target vessel revascularization rate than treatment with ZES.

Gepubliceerd: Catheter Cardiovasc Interv. 2020;96(5):E508-e15.
Impact factor: 2.044; Q3

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6. Thin, very thin, or ultrathin-strut biodegradable or durable polymer-coated drug-eluting stents
Buiten RA, Zocca P, von Birgelen C.

Purpose of Review: The current article will review recently published clinical studies that evaluate very thin or ultrathin-strut drug-eluting stents (DES), focusing on major randomized clinical trials in broad patient populations.
Recent Findings: Multiple randomized trials recently assessed the clinical performance of novel very thin to ultrathin-strut DES. Most randomized trials established noninferiority of the novel device. To date, only one major randomized clinical trial (i.e., BIOFLOW V) showed superiority of an ultrathin-strut biodegradable polymer-coated sirolimus-eluting stent over a very thin-strut durable polymer-coated everolimus-eluting stent in a relatively broad patient population. There are signals that the same ultrathin-strut biodegradable polymer-coated sirolimus-eluting stent may improve clinical outcome in specific patient populations. For example, in the randomized BIOSTEMI trial, 1-year superiority of the ultrathin-strut DES was found in patients presenting with an acute ST-segment elevation myocardial infarction. Yet,

substudies of large randomized trials that assessed patients with small-vessel treatment showed equivocal results.
Summary: Although two randomized trials showed advantages for ultrathin-strut DES, other clinical trials provided no significant evidence that ultrathin-strut DES improve clinical outcome. The question whether ultrathin-strut DES may reduce the repeat revascularization risk following implantation in small vessels is a matter of further debate and future research.

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Impact factor: 2.149; Q3

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7. 1-Year Clinical Outcomes of All Comers Treated With 2 Bioresorbable Polymer-Coated Sirolimus-Eluting Stents: Propensity Score-Matched Comparison of the COMBO and Ultrathin-Strut Orsiro Stents
Chandrasekhar J, Kok MM, Kalkman DN, Aquino MB, Zocca P, Woudstra P, Beijk MA, Kerkmeijer LS, Sartori S, Baber U, Tijssen JG, Koch KT, Dangas GD, Colombo A, Pocock S, von Birgelen C, Mehran R, de Winter RJ, COMBO Collaborators and BIO-RESORT Investigators, includes van der Heijden LC, van Houwelingen KG, Stoel MG, de Man FHAF, Louwerenburg JHW, Hartmann M, Zocca P, van der Palen J, Löwik MM.

Objectives: The aim of this study was to determine 1-year safety and efficacy after treatment with the COMBO and Orsiro stents.
Background: The COMBO stainless-steel stent has an anti-CD34(+) antibody coating to capture endothelial progenitor cells, thereby promoting faster endothelialization. The Orsiro is an ultrathin-strut cobalt-chromium stent, covered by an extremely thin layer of amorphous silicon carbide to minimize ion leakage. Both devices elute sirolimus from biodegradable polymers.
Methods: For this analysis we included European patients from the COMBO collaboration, a patient-level pooling of 2 prospective all-comers registries of COMBO stent implantation (n = 2,775), and all patients randomized to the Orsiro stent (n = 1,169) from the Dutch BIO-RESORT (Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population) randomized trial. The main outcome of interest was 1-year target lesion failure, a composite of cardiac death, target vessel myocardial infarction, and clinically driven target lesion revascularization evaluated using propensity score-matched analysis.
Results: At baseline, COMBO patients were older and had more insulin-treated diabetes, renal insufficiency, and other comorbidities. However, Orsiro patients included more current smokers and more acute coronary syndrome presentations. Orsiro patients also received longer stents and had more complex target lesions. After propensity score-matched analysis (n = 862/arm), 1-year target lesion failure occurred in 4.1% of COMBO-treated and 2.7% of Orsiro-treated patients (hazard ratio: 1.55; 95% confidence interval: 0.92 to 2.62; p = 0.10). Definite stent thrombosis occurred in 0.5% of COMBO-treated and 0.5% of Orsiro-treated patients (p = 0.99).
Conclusions: A propensity score-matched comparison of all comers treated with the COMBO or Orsiro stent showed no statistically significant differences. Stent thrombosis risk was low and similar between the stents. (Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population [BIO-RESORT], NCT01674803; MASCOT-Post Marketing Registry

[MASCOT], NCT02183454; Prospective Registry to Assess the Long-term Safety and Performance of the Combo Stent [REMEDEE Reg], NCT01874002).

Gepubliceerd: JACC Cardiovasc Interv. 2020;13(7):820-30.
Impact factor: 8.432; Q1

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8. BuMA Supreme biodegradable polymer sirolimus-eluting stent versus a durable polymer zotarolimus-eluting coronary stent: three-year clinical outcomes of the PIONEER trial
Chang CC, Kogame N, Asano T, von Birgelen C, Sabaté M, Onuma Y, Serruys PW.

Gepubliceerd: EuroIntervention. 2020;16(11):e900-e3.
Impact factor: 3.993; Q2

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9. Impact of COVID-19 pandemic and diabetes on mechanical reperfusion in patients with STEMI: insights from the ISACS STEMI COVID 19 Registry
De Luca G, Cercek M, Jensen LO, Vavlukis M, Calmac L, Johnson T, Roura IFG, Ganyukov V, Wojakowski W, von Birgelen C, Versaci F, Ten Berg J, Laine M, Dirksen M, Casella G, Kala P, Díez Gil JL, Becerra V, De Simone C, Carrill X, Scoccia A, Lux A, Kovarnik T, Davlouros P, Gabrielli G, Flores Rios X, Bakraceski N, Levesque S, Guiducci V, Kidawa M, Marinucci L, Zilio F, Galasso G, Fabris E, Menichelli M, Manzo S, Caiazzo G, Moreu J, Sanchis Forés J, Donazzan L, Vignali L, Teles R, Bosa Ojeda F, Lehtola H, Camacho-Freiere S, Kraaijeveld A, Antti Y, Boccalatte M, Martínez-Luengas IL, Scheller B, Alexopoulos D, Uccello G, Faurie B, Gutierrez Barrios A, Wilbert B, Cortese G, Moreno R, Parodi G, Kedhi E, Verdoia M.

Background: It has been suggested the COVID pandemic may have indirectly affected the treatment and outcome of STEMI patients, by avoidance or significant delays in contacting the emergency system. No data have been reported on the impact of diabetes on treatment and outcome of STEMI patients, that was therefore the aim of the current subanalysis conducted in patients included in the International Study on Acute Coronary Syndromes-ST Elevation Myocardial Infarction (ISACS-STEMI) COVID-19.
Methods: The ISACS-STEMI COVID-19 is a retrospective registry performed in European centers with an annual volume of > 120 primary percutaneous coronary intervention (PCI) and assessed STEMI patients, treated with primary PCI during the same periods of the years 2019 versus 2020 (March and April). Main outcomes are the incidences of primary PCI, delayed treatment, and in-hospital mortality.
Results: A total of 6609 patients underwent primary PCI in 77 centers, located in 18 countries. Diabetes was observed in a total of 1356 patients (20.5%), with similar proportion between 2019 and 2020. During the pandemic, there was a significant reduction in primary PCI as compared to 2019, similar in both patients with (Incidence rate ratio (IRR) 0.79 (95% CI: 0.73-0.85, p < 0.0001) and without diabetes (IRR 0.81 (95% CI: 0.78-0.85, p < 0.0001) (p int = 0.40). We observed a significant heterogeneity among centers in the population with and without diabetes (p < 0.001, respectively). The heterogeneity among centers was not related to the incidence of death due to COVID-19 in both groups of patients. Interaction was observed for Hypertension (p = 0.024) only in absence of diabetes. Furthermore, the pandemic was

independently associated with a significant increase in door-to-balloon and total ischemia times only among patients without diabetes, which may have contributed to the higher mortality, during the pandemic, observed in this group of patients.
Conclusions: The COVID-19 pandemic had a significant impact on the treatment of patients with STEMI, with a similar reduction in primary PCI procedures in both patients with and without diabetes. Hypertension had a significant impact on PCI reduction only among patients without diabetes. We observed a significant increase in ischemia time and door-to-balloon time mainly in absence of diabetes, that contributed to explain the increased mortality observed in this group of patients during the pandemic.
Trial registration number: NCT04412655.

Gepubliceerd: Cardiovasc Diabetol. 2020;19(1):215.
Impact factor: 7.332; Q1

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10. Impact of COVID-19 Pandemic on Mechanical Reperfusion for Patients With STEMI
De Luca G, Verdoia M, Cercek M, Jensen LO, Vavlukis M, Calmac L, Johnson T, Ferrer GR, Ganyukov V, Wojakowski W, Kinnaird T, von Birgelen C, Cottin Y, A I, Tuccillo B, Versaci F, Royaards KJ, Berg JT, Laine M, Dirksen M, Siviglia M, Casella G, Kala P, Díez Gil JL, Banning A, Becerra V, De Simone C, Santucci A, Carrillo X, Scoccia A, Amoroso G, Lux A, Kovarnik T, Davlouros P, Mehilli J, Gabrielli G, Rios XF, Bakraceski N, Levesque S, Cirrincione G, Guiducci V, Kidawa M, Spedicato L, Marinucci L, Ludman P, Zilio F, Galasso G, Fabris E, Menichelli M, Garcia-Touchard A, Manzo S, Caiazzo G, Moreu J, Forés JS, Donazzan L, Vignali L, Teles R, Benit E, Agostoni P, Bosa Ojeda F, Lehtola H, Camacho-Freiere S, Kraaijeveld A, Antti Y, Boccalatte M, Deharo P, Martínez-Luengas IL, Scheller B, Alexopoulos D, Moreno R, Kedhi E, Uccello G, Faurie B, Gutierrez Barrios A, Di Uccio FS, Wilbert B, Smits P, Cortese G, Parodi G, Dudek D.

Background: The fear of contagion during the coronavirus disease-2019 (COVID-19) pandemic may have potentially refrained patients with ST-segment elevation myocardial infarction (STEMI) from accessing the emergency system, with subsequent impact on mortality.
Objectives: The ISACS-STEMI COVID-19 registry aims to estimate the true impact of the COVID-19 pandemic on the treatment and outcome of patients with STEMI treated by primary percutaneous coronary intervention (PPCI), with identification of "at-risk" patient cohorts for failure to present or delays to treatment.
Methods: This retrospective registry was performed in European high-volume PPCI centers and assessed patients with STEMI treated with PPPCI in March/April 2019 and 2020. Main outcomes are the incidences of PPCI, delayed treatment, and in-hospital mortality.
Results: A total of 6,609 patients underwent PPCI in 77 centers, located in 18 countries. In 2020, during the pandemic, there was a significant reduction in PPCI as compared with 2019 (incidence rate ratio: 0.811; 95% confidence interval: 0.78 to 0.84; $p < 0.0001$). The heterogeneity among centers was not related to the incidence of death due to COVID-19. A significant interaction was observed for patients with arterial hypertension, who were less frequently admitted in 2020 than in 2019. Furthermore, the pandemic was associated with a significant increase in door-to-

balloon and total ischemia times, which may have contributed to the higher mortality during the pandemic.
Conclusions: The COVID-19 pandemic had significant impact on the treatment of patients with STEMI, with a 19% reduction in PPCI procedures, especially among patients suffering from hypertension, and a longer delay to treatment, which may have contributed to the increased mortality during the pandemic. (Primary Angioplasty for STEMI During COVID-19 Pandemic [ISACS-STEMI COVID-19] Registry; NCT04412655).

Gepubliceerd: J Am Coll Cardiol. 2020;76(20):2321-30.
Impact factor: 20.589; Q1

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11. Standardized pulmonary vein isolation workflow to enclose veins with contiguous lesions: the multicentre VISTAX trial
Duytschaever M, Vijgen J, De Potter T, Scherr D, Van Herendael H, Knecht S, Kobza R, Berte B, Sandgaard N, Albenque JP, Szeplaki G, Stevenhagen YJ, Taghji P, Wright M, Macours N, Gupta D.

Aims: To evaluate the safety and effectiveness of pulmonary vein isolation in paroxysmal atrial fibrillation (PAF) using a standardized workflow aiming to enclose the veins with contiguous and optimized radiofrequency lesions.
Methods and Results: This multicentre, prospective, non-randomized study was conducted at 17 European sites. Pulmonary vein isolation was guided by VISITAG SURPOINT (VS target ≥550 on the anterior wall; ≥400 on the posterior wall) and intertag distance (≤6 mm). Atrial arrhythmia recurrence was stringently monitored with weekly and symptom-driven transtelephonic monitoring on top of standard-of-care monitoring (24-h Holter and 12-lead electrocardiogram at 3, 6, and 12 months follow-up). Three hundred and forty participants with drug refractory PAF were enrolled. Acute effectiveness (first-pass isolation proof to a 30-min wait period and adenosine challenge) was 82.4% [95% confidence interval (CI) 77.4-86.7%]. At 12-month follow-up, the rate of freedom from any documented atrial arrhythmia was 78.3% (95% CI 73.8-82.8%), while freedom from atrial arrhythmia by standard-of-care monitoring was 89.4% (95% CI 78.8-87.0%). Freedom fromrepeat ablations by the Kaplan-Meier analysis was 90.4% during 12 months of follow-up. Of the 34 patients with repeat ablations, 14 (41.2%) demonstrated full isolation of all pulmonary vein circles. Primary adverse event (PAE) rate was 3.6% (95% CI 1.9-6.3%).
Conclusions: The VISTAX trial demonstrated that a standardized PAF ablation workflow aiming for contiguous lesions leads to low rates of PAEs, high acute first-pass isolation rates, and 12-month freedom from arrhythmias approaching 80%. Further research is needed to improve the reproducibility of the outcomes across a wider range of centres.Clinical trial registration: ClinicalTrials.gov, number NCT03062046

Gepubliceerd: Europace. 2020;22(11):1645-52.
Impact factor: 4.045; Q2

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12. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial

Gimbel M, Qaderdan K, Willemsen L, Hermanides R, Bergmeijer T, de Vrey E, Heestermans T, Tjon Joe Gin M, Waalewijn R, Hofma S, den Hartog F, Jukema W, von Birgelen C, Voskuil M, Kelder J, Deneer V, Ten Berg J.

Background: Current guidelines recommend potent platelet inhibition with ticagrelor or prasugrel in patients after an acute coronary syndrome. However, data about optimal platelet inhibition in older patients are scarce. We aimed to investigate the safety and efficacy of clopidogrel compared with ticagrelor or prasugrel in older patients with non-ST-elevation acute coronary syndrome (NSTE-ACS).
Methods: We did the open-label, randomised controlled POPular AGE trial in 12 sites (ten hospitals and two university hospitals) in the Netherlands. Patients aged 70 years or older with NSTE-ACS were enrolled and randomly assigned in a 1:1 ratio using an internet-based randomisation procedure with block sizes of six to receive a loading dose of clopidogrel 300 mg or 600 mg, or ticagrelor 180 mg or prasugrel 60 mg, and then a maintenance dose for the duration of 12 months (clopidogrel 75 mg once daily, ticagrelor 90 mg twice daily, or prasugrel 10 mg once daily) on top of standard care. Patient and treating physicians were aware of the allocated treatment strategy, but the outcome assessors were masked to treatment allocation. Primary bleeding outcome consisted of PLATelet inhibition and patient Outcomes (PLATO; major or minor bleeding [superiority hypothesis]). Co-primary net clinical benefit outcome consisted of all-cause death, myocardial infarction, stroke, PLATO major and minor bleeding (non-inferiority hypothesis, margin of 2%). Follow-up duration was 12 months. Analyses were done on intention-to-treat basis. This trial is registered with the Netherlands Trial Register (NL3804), ClinicalTrials.gov (NCT02317198), and EudraCT (2013-001403-37).
Findings: Between June 10, 2013, and Oct 17, 2018, 1002 patients were randomly assigned to clopidogrel (n=500) or ticagrelor or prasugrel (n=502). Because 475 (95%) patients received ticagrelor in the ticagrelor or prasugrel group, we will refer to this group as the ticagrelor group. Premature discontinuation of the study drug occurred in 238 (47%) of 502 ticagrelor group patients randomly assigned to ticagrelor, and in 112 (22%) of 500 patients randomly assigned to clopidogrel. Primary bleeding outcome was significantly lower in the clopidogrel group (88 [18%] of 500 patients) than in the ticagrelor group (118 [24%] of 502; hazard ratio 0·71, 95% CI 0·54 to 0·94; p=0·02 for superiority). Co-primary net clinical benefit outcome was non-inferior for the use of clopidogrel (139 [28%]) versus ticagrelor (161 [32%]; absolute risk difference -4%, 95% CI -10·0 to 1·4; p=0·03 for non-inferiority). The most important reasons for discontinuation were occurrence of bleeding (n=38), dyspnoea (n=40), and the need for treatment with oral anticoagulation (n=35).
Interpretation: In patients aged 70 years or older presenting with NSTE-ACS, clopidogrel is a favourable alternative to ticagrelor, because it leads to fewer bleeding events without an increase in the combined endpoint of all-cause death, myocardial infarction, stroke, and bleeding. Clopidogrel could be an alternative P2Y12 inhibitor especially for elderly patients with a higher bleeding risk.
Funding: ZonMw.

Gepubliceerd: Lancet. 2020;395(10233):1374-81.
Impact factor: 60.390; Q1

13. Ticagrelor Versus Clopidogrel in Older Patients with NSTE-ACS Using Oral Anticoagulation: A Sub-Analysis of the POPular Age Trial
Gimbel ME, Tavenier AH, Bor W, Hermanides RS, de Vrey E, Heestermans T, Gin MTJ, Waalewijn R, Hofma S, den Hartog F, Jukema W, von Birgelen C, Voskuil M, Kelder J, Deneer V, Ten Berg JM.

There are no randomised data on which antiplatelet agent to use in elderly patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) and an indication for oral anticoagulation (OAC). The randomised POPular Age trial, in patients of 70 years or older with NSTE-ACS, showed a reduction in bleeding without increasing thrombotic events in patients using clopidogrel as compared to ticagrelor. In this sub-analysis of the POPular AGE trial, we compare clopidogrel with ticagrelor in patients with a need for oral anticoagulation. The follow-up duration was one year. The primary bleeding outcome was Platelet Inhibition and Patient Outcomes (PLATO) major and minor bleeding. The primary thrombotic outcome consisted of cardiovascular death, myocardial infarction and stroke. The primary net clinical benefit outcome was a composite of all-cause death, myocardial infarction, stroke, and PLATO major and minor bleeding. A total of 184/1011 (18.2%) patients on OAC were included in this subanalysis; 83 were randomized to clopidogrel and 101 to ticagrelor. The primary bleeding outcome was lower in the clopidogrel group (17/83, 20.9%) compared to the ticagrelor group (33/101, 33.5%; p = 0.051), as was the thrombotic outcome (7/83, 8.4% vs. 19/101, 19.2%; p = 0.035) and the primary net clinical benefit outcome (23/83, 27.7% vs. 49/101, 48.5%; p = 0.003). In this subgroup of patients using OAC, clopidogrel reduced PLATO major and minor bleeding compared to ticagrelor without increasing thrombotic risk. This analysis therefore suggests that, in line with the POPular Age trial, clopidogrel is a better option than ticagrelor in NSTE-ACS patients ≥70 years using OAC.

Gepubliceerd: J Clin Med. 2020;9(10).
Impact factor: 3.303; Q1

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14. Prognostic Impact of Race in Patients Undergoing PCI: Analysis From 10 Randomized Coronary Stent Trials
Golomb M, Redfors B, Crowley A, Smits PC, Serruys PW, von Birgelen C, Madhavan MV, Ben-Yehuda O, Mehran R, Leon MB, Stone GW.

Objectives: The aim of this study was to assess race-based differences in patients undergoing percutaneous coronary intervention from a large pooled database of randomized controlled trials. **Background:** Data on race-based outcomes after percutaneous coronary intervention are limited, deriving mainly from registries and single-center studies.
Methods: Baseline characteristics and outcomes at 30 days, 1 year, and 5 years were assessed across different races, from an individual patient data pooled analysis from 10 randomized trials. Endpoints of interest included death, myocardial infarction, and major adverse cardiac events (defined as cardiac death, myocardial infarction, or ischemia-driven target lesion revascularization). Multivariate Cox proportional hazards

regression was performed to assess associations between race and outcomes, controlling for differences in 12 baseline covariates.
Results: Among 22,638 patients, 20,585 (90.9%) were white, 918 (4.1%) were black, 404 (1.8%) were Asian, and 473 (2.1%) were Hispanic. Baseline and angiographic characteristics differed among groups. Five-year major adverse cardiac event rates were 18.8% in white patients (reference group), compared with 23.9% in black patients (p = 0.0009), 11.2% in Asian patients (p = 0.0007), and 21.5% in Hispanic patients (p = 0.07). Multivariate analysis demonstrated an independent association between black race and 5-year risk for major adverse cardiac events (hazard ratio: 1.28; 95% confidence interval: 1.05 to 1.57; p = 0.01).
Conclusions: In the present large-scale individual patient data pooled analysis, comorbidities were significantly more frequent in minority-group patients than in white patients enrolled in coronary stent randomized controlled trials. After accounting for these differences, black race was an independent predictor of worse outcomes, whereas Hispanic ethnicity and Asian race were not. Further research examining race-based outcomes after percutaneous coronary intervention is warranted to understand these differences.

Gepubliceerd: JACC Cardiovasc Interv. 2020;13(13):1586-95.
Impact factor: 8.432; Q1

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15. Coronary Calcification and Long-Term Outcomes According to Drug-Eluting Stent Generation
Guedeney P, Claessen BE, Mehran R, Mintz GS, Liu M, Sorrentino S, Giustino G, Farhan S, Leon MB, Serruys PW, Smits PC, von Birgelen C, Ali ZA, Généreux P, Redfors B, Madhavan MV, Ben-Yehuda O, Stone GW.

Objectives: The aim of this study was to evaluate the long-term impact of coronary artery calcification (CAC) on outcomes after percutaneous coronary intervention and the respective performance of first- and second-generation drug-eluting stents (DES).
Background: Whether contemporary DES have improved the long-term prognosis after percutaneous coronary intervention in lesions with severe CAC is unknown.
Methods: Individual patient data were pooled from 18 randomized trials evaluating DES, categorized according to the presence of angiography core laboratory-confirmed moderate or severe CAC. Major endpoints were the patient-oriented composite endpoint (death, myocardial infarction [MI], or any revascularization) and the device-oriented composite endpoint of target lesion failure (cardiac death, target vessel MI, or ischemia-driven target lesion revascularization). Multivariate Cox proportional regression with study as a random effect was used to assess 5-year outcomes.
Results: A total of 19,833 patients were included. Moderate or severe CAC was present in 1 or more target lesions in 6,211 patients (31.3%) and was associated with increased 5-year risk for the patient-oriented composite endpoint (adjusted hazard ratio [adjHR]: 1.12; 95% confidence interval [CI]: 1.05 to 1.20) and target lesion failure (adjHR: 1.21; 95% CI: 1.09 to 1.34), as well as death, MI, and ischemia-driven target lesion revascularization. In patients with CAC, use of second-generation DES compared with first-generation DES was associated with reductions in the 5-year risk for the patient-oriented composite endpoint (adjHR: 0.88; 95% CI: 0.78 to 1.00) and target lesion failure (adjHR: 0.73; 95% CI: 0.61 to 0.87), as well as death or MI,

ischemia-driven target lesion revascularization, and stent thrombosis. The relative treatment effects of second-generation compared with first-generation DES were consistent in patients with and without moderate or severe CAC, although outcomes were consistently better with contemporary devices.
Conclusions: In this large-scale study, percutaneous coronary intervention of target lesion moderate or severe CAC was associated with adverse patient-oriented and device-oriented adverse outcomes at 5 years. These detrimental effects were mitigated with second-generation DES.

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Impact factor: 8.432; Q1

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16. Sustained Safety and Performance of the Second-Generation Sirolimus-Eluting Absorbable Metal Scaffold: Pooled Outcomes of the BIOSOLVE-II and -III Trials at 3 Years
Haude M, Ince H, Kische S, Toelg R, Van Mieghem NM, Verheye S, von Birgelen C, Christiansen EH, Barbato E, Garcia-Garcia HM, Waksman R.

Background/Purpose: To avoid long-term effects associated with permanent implants, bioresorbable vascular scaffolds were developed, as they provide transient vessel support and disappear thereafter. The aim of the BIOSOLVE-II and -III studies was to assess the safety and performance of a magnesium-based sirolimus-eluting scaffold; we report the clinical outcomes at 3 years, 2 years after scaffold resorption.
Methods/Materials: BIOSOLVE-II and BIOSOLVE-III are international, prospective multi-center studies, including 184 patients with 189 de novo lesions and stable or unstable angina, or documented silent ischemia. Acute myocardial infarction, 3-vessel coronary artery disease, and heavily calcified lesions were excluded. Antiplatelet therapy was recommended for 6 months.
Results: Patients were 65.5 ± 10.8 years old, and lesions were 12.1 ± 4.5 mm long and located in vessels with a diameter of 2.7 ± 0.4 mm. More than half of the lesions (56.5%) were type B2/C lesions. At 2 years, 92.5% (160/173) of patients were symptom-free and 91.5% (151/165) at 3 years; all the other patients had stable angina. At 3 years, target lesion failure occurred in 11 patients (6.3%), consisting of 4 cardiac deaths (2.3%), one target-vessel myocardial infarction (0.6%), and 6 clinically driven target lesion revascularizations (3.4%). There was no definite or probable scaffold thrombosis.
Conclusion: In a low-risk patient population, treatment with a sirolimus-eluting magnesium bioresorbable scaffold can be considered safe, in particular with no definite or probable scaffold thrombosis.
Annotated tabel of contents: BIOSOLVE-II and -III are prospective, international, multi-center studies including 184 patients with de novo lesions. At 3 years, target lesion failure was 6.3%, consisting of 4 cardiac deaths (2.3%), one target-vessel myocardial infarction (0.6%), and 6 clinically driven target lesion revascularizations (3.4%). There was no definite or probable scaffold thrombosis.

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Impact factor: nvt; nvt

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17. Safety and performance of the second-generation drug-eluting absorbable metal scaffold (DREAMS 2G) in patients with de novo coronary lesions: three-year clinical results and angiographic findings of the BIOSOLVE-II first-in-man trial

Haude M, Ince H, Toelg R, Lemos PA, von Birgelen C, Christiansen EH, Wijns W, Neumann FJ, Eeckhout E, Garcia-Garcia HM, Waksman R.

Aims: We aimed to evaluate the safety and performance of a magnesium-based sirolimus-eluting metal scaffold at three-year follow-up to assess vessel response two years beyond scaffold resorption.
Methods and Results: BIOSOLVE-II is an international, multicentre first-in-man study, including 123 patients with de novo lesions. Predilatation was mandatory and post-dilatation was left to the discretion of the investigators. Dual antiplatelet therapy was recommended for six months. At three years, 91.1% of patients were angina-free and 8.0% were on dual antiplatelet therapy. The target lesion failure rate was 6.8% (n=8: two cardiac deaths, one target vessel myocardial infarction and five target lesion revascularisations). No probable or definite scaffold thrombosis was observed. Imaging follow-up was voluntary and serial angiographic assessment at 6, 12, and 36 months was available in 25 patients. In these, a slight increase in in-segment and in-scaffold late lumen loss and diameter stenosis was observed between 12 and 36 months (by 0.11±0.28 mm and 0.13±0.30 mm for late lumen loss, and by 3.8±10.1% and 4.1±10.2% for diameter stenosis).
Conclusions: Two years beyond the resorption period of a sirolimus-eluting bioresorbable metal scaffold built from a proprietary magnesium alloy, complication rates remained low. In the patients with serial angiographic assessment, late lumen loss and diameter stenosis did not increase substantially beyond the resorption period.

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Impact factor: 3.993; Q2

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18. Comparison of clinical outcomes between Magmaris and Orsiro drug eluting stent at 12 months: Pooled patient level analysis from BIOSOLVE II-III and BIOFLOW II trials

Hideo-Kajita A, Garcia-Garcia HM, Kolm P, Azizi V, Ozaki Y, Dan K, Ince H, Kische S, Abizaid A, Töelg R, Lemos PA, Van Mieghem NM, Verheye S, von Birgelen C, Christiansen EH, Wijns W, Lefèvre T, Windecker S, Waksman R, Haude M.

Background: The aim of this study was to compare the 12-month clinical outcomes of patients treated with Magmaris or Orsiro. Second generation drug-eluting absorbable metal scaffold Magmaris (Dreams 2G) has proved to be safe and effective in the BIOSOLVE-II study. Similarly, biodegradable polymer sirolimus-eluting stent, Orsiro has shown notable clinical results even in all-comer populations.
Methods: Magmaris group patients were taken from the BIOSOLVE-II and BIOSOLVE-III trials, while the patients from Orsiro group were enrolled in BIOFLOW-II trial. The primary outcome was explored using a time-to-event assessment of the unadjusted clinical outcomes for target lesion failure (TLF) at 12 months, followed by a multivariate analysis adjusting for all the significantly different covariates between the groups.

Results: The study population consisted of 482 patients (521 lesions), 184 patients (189 lesions) in Magmaris group and 298 patients (332 lesions) in Orsiro group. The mean age was 65.5 ± 10.8 and 62.7 ± 10.4 years in Magmaris and Orsiro groups, respectively (p = 0.005). Magmaris and Orsiro unadjusted TLF rates were 6.0 and 6.4% with no significant difference between the groups (p = 0.869). In the multivariate analysis, there were no meaningful differences between Magmaris and Orsiro groups. Finally, none of the groups presented device thrombosis cases at 12 months.
Conclusion: At 12 months there were no significant differences between Magmaris and Orsiro groups neither in the unadjusted assessment nor in the multivariate analysis for target lesion failure. These results should be taken as hypothesis generating and may warrant a head to head comparison on a randomized fashion.

Gepubliceerd: Int J Cardiol. 2020;300:60-5.
Impact factor: 3.229; Q2

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19. Everolimus-eluting bioresorbable scaffolds and metallic stents in diabetic patients: a patient-level pooled analysis of the prospective ABSORB DM Benelux Study, TWENTE and DUTCH PEERS
Hommels TM, Hermanides RS, Berta B, Fabris E, De Luca G, Ploumen EH, von Birgelen C, Kedhi E.

Background: Several studies compared everolimus-eluting bioresorbable scaffolds (EE-BRS) with everolimus-eluting stents (EES), but only few assessed these devices in patients with diabetes mellitus. AIM: To evaluate the safety and efficacy outcomes of all-comer patients with diabetes mellitus up to 2 years after treatment with EE-BRS or EES.
Methods: We performed a post hoc pooled analysis of patient-level data in diabetic patients who were treated with EE-BRS or EES in 3 prospective clinical trials: The ABSORB DM Benelux Study (NTR5447), TWENTE (NTR1256/NCT01066650) and DUTCH PEERS (NTR2413/NCT01331707). Primary endpoint of the analysis was target lesion failure (TLF): a composite of cardiac death, target vessel myocardial infarction or clinically driven target lesion revascularization. Secondary endpoints included major adverse cardiac events (MACE): a composite of all-cause death, any myocardial infarction or clinically driven target vessel revascularization, as well as definite or probable device thrombosis (ST).
Results: A total of 499 diabetic patients were assessed, of whom 150 received EE-BRS and 249 received EES. Total available follow-up was 222.6 patient years (PY) in the EE-BRS and 464.9 PY in the EES group. The adverse events rates were similar in both treatment groups for TLF (7.2 vs. 5.2 events per 100 PY, p = 0.39; adjusted hazard ratio (HR) = 1.48 (95% confidence interval (CI): 0.77-2.87), p = 0.24), MACE (9.1 vs. 8.3 per 100 PY, p = 0.83; adjusted HR = 1.23 (95% CI: 0.70-2.17), p = 0.47), and ST (0.9 vs. 0.6 per 100 PY, p > 0.99).
Conclusion: In this patient-level pooled analysis of patients with diabetes mellitus from 3 clinical trials, EE-BRS showed clinical outcomes that were quite similar to EES.

Gepubliceerd: Cardiovasc Diabetol. 2020;19(1):165.
Impact factor: Impact factor: 7.332; Q1

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20. The 2010s in clinical drug-eluting stent and bioresorbable scaffold research: a Dutch perspective
Kawashima H, Zocca P, Buiten RA, Smits PC, Onuma Y, Wykrzykowska JJ, de Winter RJ, von Birgelen C, Serruys PW.

Dutch researchers were among the first to perform clinical studies in bare metal coronary stents, the use of which was initially limited by a high incidence of in-stent restenosis. This problem was greatly solved by the introduction of drug-eluting stents (DES). Nevertheless, enthusiasm about first-generation DES was subdued by discussions about a higher risk of very-late stent thrombosis and mortality, which stimulated the development, refinement, and rapid adoption of new DES with more biocompatible durable polymer coatings, biodegradable polymer coatings, or no coating at all. In terms of clinical DES research, the 2010s were characterised by numerous large-scale randomised trials in all-comers and patients with minimal exclusion criteria. Bioresorbable scaffolds (BRS) were developed and investigated. The Igaki-Tamai scaffold without drug elution was clinically tested in the Netherlands in 1999, followed by an everolimus-eluting BRS (Absorb) which showed favourable imaging and clinical results. Afterwards, multiple clinical trials comparing Absorb and its metallic counterpart were performed, revealing an increased rate of scaffold thrombosis during follow-up. Based on these studies, the commercialisation of the device was subsequently halted. Novel technologies are being developed to overcome shortcomings of first-generation BRS. In this narrative review, we look back on numerous devices and on the DES and BRS trials reported by Dutch researchers.

Gepubliceerd: Neth Heart J. 2020;28(Suppl 1):78-87.
Impact factor: 1.933; Q3

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21. Involving the patient's perspective and preferences concerning coronary angiography and percutaneous coronary intervention
Kok MM, von Birgelen C.

Gepubliceerd: EuroIntervention. 2020;15(14):1228-31.
Impact factor: 3.993; Q2

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22. Long-Term Outcomes in Women and Men Following Percutaneous Coronary Intervention
Kosmidou I, Leon MB, Zhang Y, Serruys PW, von Birgelen C, Smits PC, Ben-Yehuda O, Redfors B, Madhavan MV, Maehara A, Mehran R, Stone GW.

Background: Studies examining sex-related outcomes following percutaneous coronary intervention (PCI) have reported conflicting results.
Objectives: The purpose of this study was to examine the sex-related risk of 5-year cardiovascular outcomes after PCI.
Methods: The authors pooled patient-level data from 21 randomized PCI trials and assessed the association between sex and major adverse cardiac events (MACE) (cardiac death, myocardial infarction [MI], or ischemia-driven target lesion revascularization [ID-TLR]) as well as its individual components at 5 years.

Results: Among 32,877 patients, 9,141 (27.8%) were women. Women were older and had higher body mass index, more frequent hypertension and diabetes, and less frequent history of surgical or percutaneous revascularization compared with men. By angiographic core laboratory analysis, lesions in women had smaller reference vessel diameter and shorter lesion length. At 5 years, women had a higher unadjusted rate of MACE (18.9% vs. 17.7%; p = 0.003), all-cause death (10.4% vs. 8.7%; p = 0.0008), cardiac death (4.9% vs. 4.0%; p = 0.003) and ID-TLR (10.9% vs. 10.2%; p = 0.02) compared with men. By multivariable analysis, female sex was an independent predictor of MACE (hazard ratio [HR:]: 1.14; 95% confidence interval [CI:]: 1.01 to 1.30; p = 0.04) and ID-TLR (HR: 1.23; 95% CI: 1.05 to 1.44; p = 0.009) but not all-cause death (HR: 0.91; 95% CI: 0.75 to 1.09; p = 0.30) or cardiac death (HR: 0.97; 95% CI: 0.73 to 1.29; p = 0.85).
Conclusions: In the present large-scale, individual patient data pooled analysis of contemporary PCI trials, women had a higher risk of MACE and ID-TLR compared with men at 5 years following PCI.

Gepubliceerd: J Am Coll Cardiol. 2020;75(14):1631-40.
Impact factor: 20.589; Q1

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23. Coronary Angiography After Cardiac Arrest Without ST Segment Elevation: One-Year Outcomes of the COACT Randomized Clinical Trial
Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen MM, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak RR, Vlachojannis GJ, Eikemans BJW, van der Harst P, van der Horst ICC, Voskuil M, van der Heijden JJ, Beishuizen A, Stoel M, Camaro C, van der Hoeven H, Henriques JP, Vlaar APJ, Vink MA, van den Bogaard B, Heestermans T, de Ruijter W, Delnoij TSR, Crijns H, Jessurun GAJ, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, Spoormans EM, van de Ven PM, Oudemans-van Straaten HM, van Royen N.

Importance: Ischemic heart disease is a common cause of cardiac arrest. However, randomized data on long-term clinical outcomes of immediate coronary angiography and percutaneous coronary intervention (PCI) in patients successfully resuscitated from cardiac arrest in the absence of ST segment elevation myocardial infarction (STEMI) are lacking.
Objective: To determine whether immediate coronary angiography improves clinical outcomes at 1 year in patients after cardiac arrest without signs of STEMI, compared with a delayed coronary angiography strategy.
Design, Setting, and Participants: A prespecified analysis of a multicenter, open-label, randomized clinical trial evaluated 552 patients who were enrolled in 19 Dutch centers between January 8, 2015, and July 17, 2018. The study included patients who experienced out-of-hospital cardiac arrest with a shockable rhythm who were successfully resuscitated without signs of STEMI. Follow-up was performed at 1 year. Data were analyzed, using the intention-to-treat principle, between August 29 and October 10, 2019.
Interventions: Immediate coronary angiography and PCI if indicated or coronary angiography and PCI if indicated, delayed until after neurologic recovery.

Main Outcomes and Measures: Survival, myocardial infarction, revascularization, implantable cardiac defibrillator shock, quality of life, hospitalization for heart failure, and the composite of death or myocardial infarction or revascularization after 1 year.
Results: At 1 year, data on 522 of 552 patients (94.6%) were available for analysis. Of these patients, 413 were men (79.1%); mean (SD) age was 65.4 (12.3) years. A total of 162 of 264 patients (61.4%) in the immediate angiography group and 165 of 258 patients (64.0%) in the delayed angiography group were alive (odds ratio, 0.90; 95% CI, 0.63-1.28). The composite end point of death, myocardial infarction, or repeated revascularization since the index hospitalization was met in 112 patients (42.9%) in the immediate group and 104 patients (40.6%) in the delayed group (odds ratio, 1.10; 95% CI, 0.77-1.56). No significant differences between the groups were observed for the other outcomes at 1-year follow-up. For example, the rate of ICD shocks was 20.4% in the immediate group and 16.2% in the delayed group (odds ratio, 1.32; 95% CI, 0.66-2.64).
Conclusions and Relevance: In this trial of patients successfully resuscitated after out-of-hospital cardiac arrest and without signs of STEMI, a strategy of immediate angiography was not found to be superior to a strategy of delayed angiography with respect to clinical outcomes at 1 year. Coronary angiography in this patient group can therefore be delayed until after neurologic recovery without affecting outcomes.
Trial registration: trialregister.nl Identifier: NTR4973.

Gepubliceerd: JAMA Cardiol. 2020;5(12):1-8.
Impact factor: 12.794; Q1

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24. Stent-Related Adverse Events >1 Year After Percutaneous Coronary Intervention

Madhavan MV, Kirtane AJ, Redfors B, Généreux P, Ben-Yehuda O, Palmerini T, Benedetto U, Biondi-Zoccai G, Smits PC, von Birgelen C, Mehran R, McAndrew T, Serruys PW, Leon MB, Pocock SJ, Stone GW.

Background: The majority of stent-related major adverse cardiovascular events (MACE) after percutaneous coronary intervention (PCI) are believed to occur within the first year. Very-late (>1-year) stent-related MACE have not been well described.
Objectives: The purpose of this study was to assess the frequency and predictors of very-late stent-related events or MACE by stent type.
Methods: Individual patient data from 19 prospective, randomized metallic stent trials maintained at a leading academic research organization were pooled. Very-late MACE (a composite of cardiac death, myocardial infarction [MI], or ischemia-driven target lesion revascularization [ID-TLR]), and target lesion failure (cardiac death, target-vessel MI, or ID-TLR) were assessed within year 1 and between 1 and 5 years after PCI with bare-metal stents (BMS), first-generation drug-eluting stents (DES1) and second-generation drug-eluting stents (DES2). A network meta-analysis was performed to evaluate direct and indirect comparisons.
Results: Among 25,032 total patients, 3,718, 7,934, and 13,380 were treated with BMS, DES1, and DES2, respectively. MACE rates within 1 year after PCI were progressively lower after treatment with BMS versus DES1 versus DES2 (17.9% vs. 8.2% vs. 5.1%, respectively, $p < 0.0001$). Between years 1 and 5, very-late MACE occurred in 9.4% of patients (including 2.9% cardiac death, 3.1% MI, and 5.1% ID-TLR). Very-late MACE occurred in 9.7%, 11.0%, and 8.3% of patients treated with

BMS, DES1, and DES2, respectively ($p < 0.0001$), linearly increasing between 1 and 5 years. Similar findings were observed for target lesion failure in 19,578 patients from 12 trials. Findings were confirmed in the network meta-analysis.
Conclusions: In this large-scale, individual patient data pooled study, very-late stent-related events occurred between 1 and 5 years after PCI at a rate of ~2%/year with all stent types, with no plateau evident. New approaches are required to improve long-term outcomes after PCI.

Gepubliceerd: J Am Coll Cardiol. 2020;75(6):590-604.
Impact factor: 20.589; Q1

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25. Long-Term Outcomes After Revascularization for Stable Ischemic Heart Disease: An Individual Patient-Level Pooled Analysis of 19 Randomized Coronary Stent Trials
Madhavan MV, Redfors B, Ali ZA, Prasad M, Shahim B, Smits PC, von Birgelen C, Zhang Z, Mehran R, Serruys PW, Maehara A, Leon MB, Kirtane AJ, Stone GW.

Background: Whether revascularization improves prognosis in stable ischemic heart disease is controversial.
Methods: Individual patient-level data from 19 prospective, randomized stent trials were pooled. Rates of 5-year major adverse cardiovascular events (MACE; a composite of cardiac death, myocardial infarction, or ischemia-driven target lesion revascularization) were assessed and compared after percutaneous coronary intervention with bare-metal stents (BMS) and first-generation and second-generation drug-eluting stents (DES1 and DES2, respectively). Poisson multivariable regression analysis was performed to identify predictors of adverse events.
Results: Among 10 987 patients treated with percutaneous coronary intervention for stable ischemic heart disease, 1550, 2776, and 6661 received BMS, DES1, and DES2, respectively. The 5-year rates of MACE progressively declined with evolution in stent technology (BMS: 24.1% versus DES1: 17.9% versus DES2: 13.4%, $P<0.0001$). However, MACE rates between 1 and 5 years increased from BMS to DES1, then declined with DES2 (BMS: 7.4% versus DES1: 10.2%, DES2: 8.5%, $P=0.02$).
Conclusions: Patients with stable ischemic heart disease remain at substantial risk for long-term MACE after revascularization with percutaneous coronary intervention, even with contemporary DES. New approaches to reduce the ongoing risk of MACE beyond 1 year after stent implantation are necessary.

Gepubliceerd: Circ Cardiovasc Interv. 2020;13(4):e008565.
Impact factor: 5.493; Q1

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26. Impact of coronary lesion complexity in percutaneous coronary intervention: one-year outcomes from the large, multicentre e-Ultimaster registry
Mohamed MO, Polad J, Hildick-Smith D, Bizeau O, Baisebenov RK, Roffi M, Íñiguez-Romo A, Chevalier B, von Birgelen C, Roguin A, Aminian A, Angioi M, Mamas MA.

Aims: The present study sought to examine the prevalence, clinical characteristics and one-year outcomes of patients undergoing percutaneous coronary intervention (PCI) to complex lesions (multivessel PCI, ≥3 stents, ≥3 lesions, bifurcation with ≥2 stents, total stent length >60 mm or chronic total occlusion [CTO]) in a prospective multicentre registry.
Methods and Results: Using the e-Ultimaster multicentre registry, a post hoc subgroup analysis was performed on 35,839 patients undergoing PCI, stratified by procedure complexity, and further by number and type of complex features. Overall, complex PCI patients (n=9,793, 27.3%) were older, more comorbid and were associated with an increased hazard ratio (HR) of the composite endpoint at one year (target lesion failure [TLF]: 1.41 [1.25; 1.59]), driven by an increased hazard of cardiac death (1.28 [1.05; 1.55]), target vessel myocardial infarction (1.48 [1.18; 1.86]) and clinically driven target lesion revascularisation. The hazard of complications increased with the rising number of complex features (3-6 vs 1-2 vs none) for all outcomes. All individual complex features were associated with an increased hazard of composite complications (except CTO) and definite/probable stent thrombosis.
Conclusions: Overall, complex PCI is associated with an increased risk of mortality and complications at one year. The number and types of complex features have differing impacts on long-term outcomes.

Gepubliceerd: EuroIntervention. 2020;16(7):603-12.
Impact factor: 3.993; Q2

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27. High incidence of (ultra)low oesophageal temperatures during cryoballoon pulmonary vein isolation for atrial fibrillation
Molenaar MMD, Hesselink T, Scholten MF, Kraaier K, Bouman DE, Brusse-Keizer M, Stevenhagen YJ, van Dessel P, Ten Haken B, Grandjean JG, van Opstal JM.

Background: Low oesophageal temperatures (OTs) during cryoballoon pulmonary vein isolation (PVI) have been associated with complications. This study assessed the incidence of low OT in clinical practice during cryoballoon PVI and verified possible predictive values for low OT.
Methods: Consecutive patients who underwent PVI using the second-generation cryoballoon were retrospectively included. The distance from the oesophagus to the different pulmonary veins (PVs) (OP distance), body mass index (BMI), sex, age, balloon temperature and application time were studied as potential predictors of low OTs. Computed tomography was performed before the procedure to determine the OP distance. OT was measured using an oesophageal temperature probe. Applications were ended prematurely if the OT reached <16 °C. Low and ultralow OT were defined as OT <20 and <16 °C respectively.
Results: Two hundred and four patients were included. Low OT was observed in 54 patients (26%) and 27 patients (13%) reached ultralow OTs. OP distance was the only predictor of low OTs after multivariate analysis. A cut-off value of 19 mm showed 96.2% sensitivity and 37.8% specificity in predicting low OTs. No clinically relevant relation was found between low OTs and BMI, age, sex, balloon temperature or application duration.
Conclusions: The incidence of low OT was 26% for cryoballoon PVI. OP distance was the only predictor of low OTs. Since an OP distance <19 mm was present in all

patients in at least one PV, we recommend routine OT measurement during PVI cryoballoon therapy to prevent oesophagus-related complications.

Gepubliceerd: Neth Heart J. 2020;28(12):662-9.
Impact factor: 1.933; Q3

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28. Shorter RSPV cryoapplications result in less phrenic nerve injury and similar 1-year freedom from atrial fibrillation
Molenaar MMD, Hesselink T, Ter Bekke RMA, Scholten MF, Manusama R, Pison L, Brusse-Keizer M, Kraaier K, Ten Haken B, Grandjean JG, Timmermans CC, van Opstal JM.

Background: In the 123-study, we prospectively assessed, in a randomized fashion, the minimal cryoballoon application time necessary to achieve pulmonary vein (PV) isolation (PVI) in patients with paroxysmal atrial fibrillation (AF) with the aim to reduce complications by shortening the application duration. The first results of this study demonstrated that shortened cryoballoon applications (<2 minutes) resulted in less phrenic nerve injury (PNI) without compromising acute isolation efficacy for the right PVs. We now report the 1-year follow-up results regarding safety and efficacy of shorter cryoballoon applications.
Methods: A total of 222 patients with AF were randomized to two applications of 1 min "short," 2 min "medium," or 3 min "long" duration, 74 per group. Recurrence of AF and PV reconduction at 1-year follow-up were assessed.
Results: The overall 1-year freedom from AF was 79% and did not differ significantly between the short, medium, and long application groups (77%, 74%, and 85% for short, medium, and long application groups, respectively; P = 0.07). In 30 patients, a redo PVI procedure was performed. For all four PVs, there was no significant difference in reconduction between the three groups. Reconduction was most common in the left superior PV (57%). The right superior PV (RSPV) showed significantly less reconduction (17%) compared to the other PVs.
Conclusions: Shortening cryoballoon applications of the RSPV to <2 minutes results in less PNI, while acute success and 1-year freedom from AF are not compromised. Therefore, shorter cryoballoon applications (especially) in the RSPV could be used to reduce PNI.

Gepubliceerd: Pacing Clin Electrophysiol. 2020;43(10):1173-9.
Impact factor: 1.303; Q4

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29. Anticoagulation with or without Clopidogrel after Transcatheter Aortic-Valve Implantation
Nijenhuis VJ, Brouwer J, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, Frambach P, De Bruyne B, van Houwelingen GK, Van Der Heyden JAS, Toušek P, van der Kley F, Buysschaert I, Schotborgh CE, Ferdinande B, van der Harst P, Roosen J, Peper J, Thielen FWF, Veenstra L, Chan Pin Yin D, Swaans MJ, Rensing B, van 't Hof AWJ, Timmers L, Kelder JC, Stella PR, Baan J, Ten Berg JM.

Background: The roles of anticoagulation alone or with an antiplatelet agent after transcatheter aortic-valve implantation (TAVI) have not been well studied.

Methods: We performed a randomized trial of clopidogrel in patients undergoing TAVI who were receiving oral anticoagulation for appropriate indications. Patients were assigned before TAVI in a 1:1 ratio not to receive clopidogrel or to receive clopidogrel for 3 months. The two primary outcomes were all bleeding and non-procedure-related bleeding over a period of 12 months. Procedure-related bleeding was defined as Bleeding Academic Research Consortium type 4 severe bleeding, and therefore most bleeding at the puncture site was counted as non-procedure-related. The two secondary outcomes were a composite of death from cardiovascular causes, non-procedure-related bleeding, stroke, or myocardial infarction at 12 months (secondary composite 1) and a composite of death from cardiovascular causes, ischemic stroke, or myocardial infarction (secondary composite 2), both tested for noninferiority (noninferiority margin, 7.5 percentage points) and superiority.
Results: Bleeding occurred in 34 of the 157 patients (21.7%) receiving oral anticoagulation alone and in 54 of the 156 (34.6%) receiving oral anticoagulation plus clopidogrel (risk ratio, 0.63; 95% confidence interval [CI], 0.43 to 0.90; P = 0.01); most bleeding events were at the TAVI access site. Non-procedure-related bleeding occurred in 34 patients (21.7%) and in 53 (34.0%), respectively (risk ratio, 0.64; 95% CI, 0.44 to 0.92; P = 0.02). Most bleeding occurred in the first month and was minor. A secondary composite 1 event occurred in 49 patients (31.2%) receiving oral anticoagulation alone and in 71 (45.5%) receiving oral anticoagulation plus clopidogrel (difference, -14.3 percentage points; 95% CI for noninferiority, -25.0 to -3.6; risk ratio, 0.69; 95% CI for superiority, 0.51 to 0.92). A secondary composite 2 event occurred in 21 patients (13.4%) and in 27 (17.3%), respectively (difference, -3.9 percentage points; 95% CI for noninferiority, -11.9 to 4.0; risk ratio, 0.77; 95% CI for superiority, 0.46 to 1.31).
Conclusions: In patients undergoing TAVI who were receiving oral anticoagulation, the incidence of serious bleeding over a period of 1 month or 1 year was lower with oral anticoagulation alone than with oral anticoagulation plus clopidogrel. (Funded by the Netherlands Organization for Health Research and Development; POPular TAVI EU Clinical Trials Register number, 2013-003125-28; ClinicalTrials.gov number, NCT02247128.).

Gepubliceerd: N Engl J Med. 2020;382(18):1696-707.
Impact factor: 74.699; Q1

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30. New-generation drug-eluting coronary stents in octogenarians: Patient-level pooled analysis from the TWENTE I-IV trials
Ploumen EH, Buiten RA, Doggen CJM, Stoel MG, van Houwelingen KG, Schotborgh CE, Jessurun GAJ, Roguin A, Danse PW, Benit E, Aminian A, Linssen GCM, de Man F, Hartmann M, Buiten DG, Kok MM, Zocca P, von Birgelen C.

Background: Patients aged ≥80 years are often treated with new-generation drug-eluting stents (DES), but data from randomized studies are scarce owing to underrepresentation in most trials. We assessed 1-year clinical outcome of octogenarians treated with new-generation DES versus younger patients.
Methods: We pooled patient-level data of 9,204 participants in the TWENTE, DUTCH PEERS, BIO-RESORT, and BIONYX (TWENTE I-IV) randomized trials. The main clinical end point was target vessel failure (TVF), a composite of cardiac death, target

vessel-related myocardial infarction (MI), or clinically indicated target vessel revascularization.
Results: The 671 octogenarian trial participants had significantly more comorbidities. TVF was higher in octogenarians than in 8,533 patients <80 years (7.3% vs 5.3%, hazard ratio [HR]: 1.36, 95% CI: 1.0-1.83, P = .04). The cardiac death rate was higher in octogenarians (3.9% vs 0.8%, P < .001). There was no significant between-group difference in target vessel MI (2.3% vs 2.3%, P = .88) and repeat target vessel revascularization (1.9% vs 2.8%, P = .16). In multivariate analyses, age ≥ 80 years showed no independent association with TVF (adjusted HR: 1.04, 95% CI: 0.76-1.42), whereas the risk of cardiac death remained higher in octogenarians (adjusted HR: 3.38, 95% CI: 2.07-5.52, P < .001). In 6,002 trial participants, in whom data on major bleeding were recorded, octogenarians (n = 459) showed a higher major bleeding risk (5.9% vs 1.9%; HR: 3.08, 95% CI: 2.01-4.74, P < .001).
Conclusions: Octogenarian participants in 4 large-scale randomized DES trials had more comorbidities and a higher incidence of the main end point TVF. Cardiac mortality was higher in octogenarians, whereas there was no increase in MI or target vessel revascularization rates. Treatment of octogenarian patients with new-generation DES appears to be safe and effective.

Gepubliceerd: Am Heart J. 2020;228:109-15.
Impact factor: 4.153; Q2

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31. Three-year clinical outcome in all-comers with "silent" diabetes, prediabetes, or normoglycemia, treated with contemporary coronary drug-eluting stents: From the BIO-RESORT Silent Diabetes study
Ploumen EH, Buiten RA, Kok MM, Doggen CJM, van Houwelingen KG, Stoel MG, de Man F, Hartmann M, Zocca P, Linssen GCM, Doelman C, Kant GD, von Birgelen C.

Background: Patients with coronary disease may have unknown diabetes or prediabetes. We evaluated 3-year outcomes after percutaneous coronary intervention (PCI) with contemporary drug-eluting stents (DES) in patients with silent diabetes, prediabetes, and normoglycemia.
Methods: All BIO-RESORT trial (NCT01674803) participants without known diabetes, enrolled at our center, were invited for oral glucose tolerance testing (OGTT) and measurements of fasting plasma glucose and glycated hemoglobin (HbA1c).
Results: OGTT detected silent diabetes in 68 (6.9%), prediabetes in 132 (13.4%), and normoglycemia in 788 (79.8%) of all 988 study participants. Follow-up was available in 986 (99.8%) patients. The main endpoint target vessel failure (TVF: cardiac death, target vessel-related myocardial infarction [MI], or target vessel revascularization) differed between groups (14.8, 9.9, and 5.6%; p = .002), driven by MI during the first 48 hr and by cardiac death (p < .001; p = .026). Between 48 hr and 3-years, there was no significant between-group difference in TVF, target vessel MI, and target vessel revascularization. Multivariable analysis demonstrated that silent diabetes was independently associated with TVF (adjusted HR: 2.52, 95%-CI: 1.26-5.03). An alternative diagnostic approach-HbA1c and fasting plasma glucose-detected silent diabetes and prediabetes in 33 (3.3%) and 217 (22.0%) patients, and normoglycemia in 738 (74.7%); TVF rates were 12.1, 7.9, and 6.0% (p = .23).

Conclusion: In patients without known diabetes, abnormal glucose metabolism by OGTT was independently associated with higher 3-year TVF rates after PCI with contemporary DES. This difference was driven by periprocedural MI and cardiac death. After the first 48 hr, the rates of TVF, target vessel MI, and target vessel revascularization were low and did not differ significantly between metabolic groups.

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Impact factor: 2.044; Q3

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32. Resolute zotarolimus-eluting stent in ST-elevation myocardial infarction (resolute-STEMI): A prespecified prospective register from the DAPT-STEMI trial
Postma W, Fabris E, Van der Ent M, Hermanides R, Buszman P, Von Birgelen C, Cook S, Wedel H, De Luca G, Delewi R, Zijlstra F, Kedhi E.

Objectives: To evaluate the safety and efficacy outcomes after primary percutaneous coronary intervention (pPCI) with second-generation Resolute™ zotarolimus-eluting stent (R-ZES) in patients enrolled in the DAPT-STEMI Trial (NCT01459627).
Background: R-ZES is one of the most used drug eluting stents worldwide. To date, the safety and efficacy data of this stent in setting of STEMI is limited.
Methods: The Resolute-STEMI is a prespecified prospective register that reports the safety and efficacy of R-ZES in setting of ST-Elevation Myocardial Infarction (STEMI) at 6 months for the following endpoints: a composite endpoint of all-cause mortality, any myocardial infarction (MI), any (unscheduled) revascularization, stroke and TIMI major bleeding, as well as target lesion failure and stent thrombosis (ST).
Results: From a total of 1,100 STEMI patients enrolled in the trial, 998 received a R-ZES. At 6 months the PE occurred in 42 (4.2%) patients. All-cause death, MI, revascularization, stroke and TIMI major bleeding was respectively 8 (0.8%), 9 (0.8%), 34 (3.4%), 2 (0.2%), and 4 (0.4%). The rate of target lesion revascularizations involving the culprit lesion was 1.1%. Target lesion failure was 1.5%. The rate of definite ST was 0.5%. The rate of both definite or probable ST was 0.7%.
Conclusions: The present analysis is the largest to date reporting short-term and mid-term clinical outcomes with the R-ZES stent in setting of STEMI. At 30 days and 6-months R-ZES has an outstanding safety and efficacy even in this high-risk category of patients.

Gepubliceerd: Catheter Cardiovasc Interv. 2020;95(4):706-10.
Impact factor: 2.044; Q3

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33. Proximal LAD Treated With Thin-Strut New-Generation Drug-Eluting Stents: A Patient-Level Pooled Analysis of TWENTE I-III
Roguin A, Buiten RA, Doggen CJM, Kobo O, Zocca P, Danse PW, Schotborgh CE, Jessurun GAJ, van Houwelingen KG, Stoel MG, Tjon Joe Gin RM, Linssen GCM, von Birgelen C.

Objectives: This study sought to assess 2-year clinical outcome following percutaneous coronary intervention (PCI) with thin-strut new-generation drug-eluting

stents (DES) in patients treated in proximal left anterior descending artery (P-LAD) versus non-P-LAD lesions.
Background: In current revascularization guidelines, P-LAD coronary artery stenosis is discussed separately, mainly because of a higher adverse event risk and benefits of bypass surgery.
Methods: The study included 6,037 patients without previous bypass surgery or left main stem involvement from the TWENTE I, II, and III randomized trials. A total of 1,607 (26.6%) patients had at least 1 DES implanted in P-LAD and were compared with 4,430 (73.4%) patients who were exclusively treated in other (non-P-LAD) segments.
Results: Two-year follow-up was available in 5,995 (99.3%) patients. At baseline, P-LAD patients had more multivessel treatment and longer total stent length. The rate of the patient-oriented composite clinical endpoint (any death, any myocardial infarction, or any revascularization) was similar in P-LAD versus non-P-LAD patients (11.4% vs. 11.6%; p = 0.87). In P-LAD patients, the rate of the device-oriented composite clinical endpoint (cardiac death, target vessel myocardial infarction, or target lesion revascularization) was higher (7.6% vs. 6.0%; p = 0.020), driven by a higher rate of target vessel myocardial infarction (4.1% vs. 2.6%; p = 0.002). However, multivariate analysis showed no independent association between stenting P-LAD lesions and clinical endpoints.
Conclusions: In this patient-level pooled analysis of 3 large-scale contemporary DES trials, treatment of P-LAD lesions was not independently associated with higher 2-year adverse clinical event rates. These results imply that separate consideration in future revascularization guidelines may not be mandatory any longer.

Gepubliceerd: JACC Cardiovasc Interv. 2020;13(7):808-16.
Impact factor: 8.432; Q1

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34. Drug-induced 'Torsade de Pointes' in a COVID-19 patient despite discontinuation of chloroquine. Importance of its long half-life: a case report
Semedo E, Kapel GF, van Opstal J, van Dessel P.

Background: Early studies have led to the repositioning of a subgroup of antimalarial agents (e.g. chloroquine and hydroxychloroquine) as antiviral treatment in coronavirus disease 2019 (COVID-19) patients. These drugs are now being prescribed based on small non-controlled studies, but larger controlled studies have yet to demonstrate the positive effect of these drugs. In addition, these drugs are also known for their QT interval-prolonging effect associated with significant morbidity and mortality. CASE
Summary: We present a case of a 66-year-old female admitted to the intensive care unit with respiratory failure due to COVID-19. She was treated with chloroquine (QTc interval at baseline was 429 ms). Despite cessation of chloroquine, but after the start of erythromycin, she developed severe QTc interval prolongation (QTc interval 550 ms) and 'Torsade de Pointes'. Two weeks after cessation of all QTc interval-prolonging drugs, the QTc interval was restored.
Discussion: The elimination half-life of chloroquine ranges from days up to weeks. Even after discontinuation of chloroquine, ECG monitoring in COVID-19 patients is warranted. We recommend observation of the QT interval after cessation of

chloroquine in cases where other potentially QT interval-prolonging drugs are introduced.

Gepubliceerd: Eur Heart J Case Rep. 2020;4(Fi1):1-5.
Impact factor: nvt; nvt

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35. Data on sex differences in one-year outcomes of out-of-hospital cardiac arrest patients without ST-segment elevation
Spoormans EM, Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, van de Ven PM, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak R, Vlachojannis GJ, Eikemans BJW, van der Harst P, van der Horst ICC, Voskuil M, van der Heijden JJ, Beishuizen A, Stoel M, Camaro C, van der Hoeven H, Henriques JP, Vlaar APJ, Vink MA, van den Bogaard B, Heestermans T, de Ruijter W, Delnoij TSR, Crijns H, Jessurun GAJ, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, Appelman Y, van Royen N.

Sex differences in out-of-hospital cardiac arrest (OHCA) patients are increasingly recognized. Although it has been found that post-resuscitated women are less likely to have significant coronary artery disease (CAD) than men, data on follow-up in these patients are limited. Data for this data in brief article was obtained as a part of the randomized controlled Coronary Angiography after Cardiac Arrest without ST-segment elevation (COACT) trial. The data supplements the manuscript "Sex differences in out-of-hospital cardiac arrest patients without ST-segment elevation: A COACT trial substudy" were it was found that women were less likely to have significant CAD including chronic total occlusions, and had worse survival when CAD was present. The dataset presented in this paper describes sex differences on interventions, implantable-cardioverter defibrillator (ICD) shocks and hospitalizations due to heart failure during one-year follow-up in patients successfully resuscitated after OHCA. Data was derived through a telephone interview at one year with the patient or general practitioner. Patients in this randomized dataset reflects a homogenous study population, which can be valuable to further build on research regarding long-term sex differences and to further improve cardiac care.

Gepubliceerd: Data Brief. 2020;33:106521.
Impact factor: nvt; nvt

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36. Platelet Inhibition, Endothelial Function, and Clinical Outcome in Patients Presenting With ST-Segment-Elevation Myocardial Infarction Randomized to Ticagrelor Versus Prasugrel Maintenance Therapy: Long-Term Follow-Up of the REDUCE-MVI Trial
van der Hoeven NW, Janssens GN, Everaars H, Nap A, Lemkes JS, de Waard GA, van de Ven PM, van Rossum AC, Escaned J, Mejia-Renteria H, Ten Cate TJF, Piek JJ, von Birgelen C, Valgimigli M, Diletti R, Riksen NP, Van Mieghem NM, Nijveldt R, van Leeuwen MAH, van Royen N.

Background: Off-target properties of ticagrelor might reduce microvascular injury and improve clinical outcome in patients with ST-segment-elevation myocardial infarction. The REDUCE-MVI (Evaluation of Microvascular Injury in Revascularized Patients

with ST-Segment-Elevation Myocardial Infarction Treated With Ticagrelor Versus Prasugrel) trial reported no benefit of ticagrelor regarding microvascular function at 1 month. We now present the follow-up data up to 1.5 years.
Methods and Results: We randomized 110 patients with ST-segment-elevation myocardial infarction to either ticagrelor 90 mg twice daily or prasugrel 10 mg once a day. Platelet inhibition and peripheral endothelial function measurements including calculation of the reactive hyperemia index and clinical follow-up were obtained up to 1.5 years. Major adverse clinical events and bleedings were scored. An intention to treat and a per-protocol analysis were performed. There were no between-group differences in platelet inhibition and endothelial function. At 1 year the reactive hyperemia index in the ticagrelor group was 0.66±0.26 versus 0.61±0.28 in the prasugrel group (P=0.31). Platelet inhibition was lower at 1 month versus 1 year in the total study population (61% [42%-81%] versus 83% [61%-95%]; P<0.001), and per-protocol platelet inhibition was higher in patients randomized to ticagrelor versus prasugrel at 1 year (91% [83%-97%] versus 82% [65%-92%]; P=0.002). There was an improvement in intention to treat endothelial function in patients randomized to ticagrelor (P=0.03) but not in patients randomized to prasugrel (P=0.88). Major adverse clinical events (10% versus 14%; P=0.54) and bleedings (47% versus 63%; P=0.10) were similar in the intention-to-treat analysis in both groups.
Conclusions: Platelet inhibition at 1 year was higher in the ticagrelor group, without an accompanying increase in bleedings. Endothelial function improved over time in ticagrelor patients, while it did not change in the prasugrel group. Clinical Trial Registration Unique Identifier: NCT02422888.

Gepubliceerd: J Am Heart Assoc. 2020;9(5):e014411.
Impact factor: 4.605; Q1

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37. The additional value of an algorithm for atrial fibrillation at the stroke unit
van der Maten G, Plas GJJ, Meijs MFL, Brouwers P, Brusse-Keizer MGJ, den Hertog HM.

Background and Purpose: The rate of newly detected (paroxysmal) atrial fibrillation (AF) during inpatient cardiac telemetry is low. The objective of this study was to evaluate the additional diagnostic yield of an automated detection algorithm for AF on telemetric monitoring compared with routine detection by a stroke unit team in patients with recent ischemic stroke or TIA.
Methods: Patients admitted to the stroke unit of Medisch Spectrum Twente with acute ischemic stroke or TIA and no history of AF were prospectively included. All patients had telemetry monitoring, routinely assessed by the stroke unit team. The ST segment and arrhythmia monitoring (ST/AR) algorithm was active, with deactivated AF alarms. After 24 h the detections were analyzed and compared with routine evaluation.
Results: Five hundred and seven patients were included (52.5% male, mean age 70.2 ± 12.9 years). Median monitor duration was 24 (interquartile range 22-27) h. In 6 patients (1.2%) routine analysis by the stroke unit team concluded AF. In 24 patients (4.7%), the ST/AR Algorithm suggested AF. Interrater reliability was low (κ, 0.388, $p < 0.001$). Suggested AF by the algorithm turned out to be false positive in 11 patients. In 13 patients (2.6%) AF was correctly diagnosed by the algorithm. None of the cases detected by routine analysis were missed by the algorithm.

Conclusions: Automated AF detection during 24-h telemetry in ischemic stroke patients is of additional value to detect paroxysmal AF compared with routine analysis by the stroke unit team alone. Automated detections need to be carefully evaluated.

Gepubliceerd: J Stroke Cerebrovasc Dis. 2020;29(8):104930.
Impact factor: 1.787; Q4

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38. Heterogeneity in Preferences for Anti-coagulant Use in Atrial Fibrillation: A Latent Class Analysis
van Til J, Oudshoorn-Groothuis C, Weernink M, von Birgelen C.

Introduction: Recent reviews on patients' preferences towards attributes of oral anti-coagulant therapy have shown that preference for convenience of therapy is heterogeneous. In this study, we used a novel approach-latent class analysis (LCA)- to assess heterogeneity.
Methods: We developed a health preference survey that consisted of 12 discrete choice questions. The following attributes of convenience were included: intake frequency; need for regular coagulation monitoring; diet or drug interactions; relation between medication and food intake; and pill type. Background questions about gender, age, current therapy [i.e., direct-acting oral anti-coagulant (DOAC) or vitamin K antagonist (VKA)], self-reported medication adherence, and pill burden were included. Mixed logit analysis (MLA) and LCA were performed. The scale-adjusted LCA model with two scale classes and four preference classes emerged as the model with the best fit and interpretability.
Results: A total of 508 patients with non-valvular atrial fibrillation from five European countries (Germany, Italy, Spain, France, and the UK) were surveyed in August 2017. The most important attributes were need for monitoring (37%) and intake frequency (27%). Patient preferences were significantly influenced by country, gender, and current anti-coagulant therapy. Four different preference classes of patients were identified in the LCA. First, most patients (57%) were in the "no need for regular coagulation monitoring" class. Current DOAC users and patients who were the least adherent to therapy were more likely to prefer no coagulation monitoring. Second, 20% of patients were in the "balanced" class of patients. Current VKA users with moderate adherence were more likely to be in this class. Patients who reported the lowest adherence were most likely in the "once daily, interactions likely" class (16%). Fourth, current VKA users and highly adherent patients were most likely to prefer therapies with a need for regular coagulation monitoring (7%).
Conclusions: This study demonstrated significant preference heterogeneity among patients with atrial fibrillation and linked these preferences to differences in background characteristics. Country of residence and currently prescribed therapy influenced patient preferences in both the MLA and LCA models.

Gepubliceerd: Patient. 2020;13(4):445-55.
Impact factor: 3.226; Q1

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39. Effect of Adding Ticagrelor to Standard Aspirin on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting (POPular CABG): A Randomized, Double-Blind, Placebo-Controlled Trial

Willemsen LM, Janssen PWA, Peper J, Soliman-Hamad MA, van Straten AHM, Klein P, Hackeng CM, Sonker U, Bekker MWA, von Birgelen C, Brouwer MA, van der Harst P, Vlot EA, Deneer VHM, Chan Pin Yin D, Gimbel ME, Beukema KF, Daeter EJ, Kelder JC, Tijssen JGP, Rensing B, van Es HW, Swaans MJ, Ten Berg JM.

Background: Approximately 15% of saphenous vein grafts (SVGs) occlude during the first year after coronary artery bypass graft surgery (CABG) despite aspirin use. The POPular CABG trial (The Effect of Ticagrelor on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting Surgery) investigated whether ticagrelor added to standard aspirin improves SVG patency at 1 year after CABG.
Methods: In this investigator-initiated, randomized, double-blind, placebo-controlled, multicenter trial, patients with ≥1 SVGs were randomly assigned (1:1) after CABG to ticagrelor or placebo added to standard aspirin (80 mg or 100 mg). The primary outcome was SVG occlusion at 1 year, assessed with coronary computed tomography angiography, in all patients that had primary outcome imaging available. A generalized estimating equation model was used to perform the primary analysis per SVG. The secondary outcome was 1-year SVG failure, which was a composite of SVG occlusion, SVG revascularization, myocardial infarction in myocardial territory supplied by a SVG, or sudden death.
Results: Among 499 randomly assigned patients, the mean age was 67.9±8.3 years, 87.1% were male, the indication for CABG was acute coronary syndrome in 31.3%, and 95.2% of procedures used cardiopulmonary bypass. Primary outcome imaging was available in 220 patients in the ticagrelor group and 223 patients in the placebo group. The SVG occlusion rate in the ticagrelor group was 10.5% (51 of 484 SVGs) versus 9.1% in the placebo group (43 of 470 SVGs), odds ratio, 1.29 [95% CI, 0.73-2.30]; P=0.38. SVG failure occurred in 35 (14.2%) patients in the ticagrelor group versus 29 (11.6%) patients in the placebo group (odds ratio, 1.22 [95% CI, 0.72-2.05]).
Conclusions: In this randomized, placebo-controlled trial, the addition of ticagrelor to standard aspirin did not reduce SVG occlusion at 1 year after CABG.
Registration: Unique identifier: NCT02352402.

Gepubliceerd: Circulation. 2020;142(19):1799-807.
Impact factor: 23.603; Q1

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40. The obesity paradox revisited: body mass index and -long-term outcomes after PCI from a large pooled patient-level database
Wolny R, Maehara A, Liu Y, Zhang Z, Mintz GS, Redfors B, Madhavan MV, Smits PC, von Birgelen C, Serruys PW, Mehran R, Leon MB, Stone GW.

Aims: The aim of this study was to evaluate the relationship between body mass index (BMI) and outcomes in patients with coronary artery disease undergoing percutaneous revascularisation.
Methods and Results: In 13 randomised trials, 22,922 patients were stratified (in kg/m2) as underweight (BMI <18.5), normal weight (18.5 ≤BMI <25, used as reference), overweight (25 ≤BMI <30), and obese (Class I [30 ≤BMI <35], Class II [35 ≤BMI <40], or Class III [BMI ≥40]). The primary endpoint was all-cause death at five years. Secondary endpoints were cardiac and non-cardiac death, target (TLR) and

non-target lesion revascularisation (NTLR), myocardial infarction (MI), and definite/probable stent thrombosis. Despite adjustment for multiple confounders, overweight and Class I obesity were associated with lower all-cause mortality versus normal weight (HR 0.83, 95% CI: 0.71-0.96, and HR 0.83, 95% CI: 0.69-0.96, respectively); however, non-cardiac death was the major contributor to this effect (HR 0.77, 95% CI: 0.63-0.94 for overweight). Conversely, cardiac mortality was higher in severely obese individuals (HR 1.62, 95% CI: 1.05-2.51 for Class III obesity). Obesity was associated with higher rates of NTLR (HR 1.28, 95% CI: 1.04-1.58 for Class II obesity) but not with TLR, MI and stent thrombosis.
Conclusions: Moderately increased BMI is associated with improved survival post PCI, mostly due to lower non-cardiac but not cardiac mortality.

Gepubliceerd: EuroIntervention. 2020;15(13):1199-208.
Impact factor: 3.993; Q2

Totale impact factor: 433.194
Gemiddelde impact factor: 10.830

Aantal artikelen 1e, 2e of laatste auteur: 14
Totale impact factor: 48.074
Gemiddelde impact factor: 3.434

Gynaecologie

1. Pregnancy outcomes in women with primary biliary cholangitis and primary sclerosing cholangitis: a retrospective cohort study
Cauldwell M, Mackie FL, Steer PJ, Henehghan MA, Baalman JH, Brennand J, Johnston T, Dockree S, Hedley C, Jarvis S, Khan S, McAuliffe FM, Mackillop L, Penna L, Smith B, Trivedi P, Verma S, Westbrook R, Winifield S, Williamson C.

Objective: To determine maternal, obstetric and neonatal outcomes in a cohort of women with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC).
Design: Retrospective cohort study.
Setting: Ten specialist centres managing pregnant women with liver disease.
POPULATION: Women with a diagnosis of PBC and PSC and a pregnancy of ≥20 completed weeks of gestation.
Methods: Retrospective case notes review.
Main Outcome Measures: Adverse outcomes were defined as: maternal - development of ascites, variceal bleeding, encephalopathy and jaundice; obstetric events - gestational hypertension, pre-eclampsia and postpartum haemorrhage; and neonatal - stillbirth, preterm delivery and admission to neonatal unit. The relationship of alanine transferase (ALT) and bile acid levels with gestation at delivery was studied.
Results: The first recorded pregnancies of 34 women with PSC and 27 women with PBC were analysed. There were 60 live births and one intrapartum stillbirth that did not occur in the context of maternal cholestasis. The overall median gestation of delivery was 38 weeks but the rate of preterm birth was 28% (17/61 deliveries), 76% (13/17) of which were spontaneous. Gestation at birth negatively correlated with maternal serum ALT concentration at booking (P = 0.017) and serum bile acid concentration during pregnancy (P = 0.016). There were no other significant correlations and maternal and neonatal outcomes were good.
Conclusions: Pregnancy in PBC and PSC is well tolerated, but women should be counselled regarding the increased risk of preterm birth. Measurement of maternal ALT and bile acids may help identify women at risk of preterm delivery. TWEETABLE ABSTRACT: Pregnancy in women with PBC and PSC is well tolerated; however, rates of preterm birth are high and are related to maternal bile acid levels.

Gepubliceerd: Bjog. 2020;127(7):876-84.
Impact factor: 4.663; Q1

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2. Maternal and neonatal outcomes in women with history of coronary artery disease
Cauldwell M, Steer PJ, von Klemperer K, Kaler M, Grixti S, Hale J, O'Heney J, Warriner D, Curtis S, Mohan AR, Dockree S, Mackillop L, Head CEG, Sterrenberg M, Wallace S, Freeman LJ, Patridge G, Baalman JH, McAuliffe FM, Simpson M, Walker N, Girling J, Siddiqui F, Bolger AP, Bredaki F, Walker F, Vause S, Gatzoulis MA, Johnson MR, Roberts A.

Background: Pregnancy outcomes in women with pre-existing coronary artery disease (CAD) are poorly described. There is a paucity of data therefore on which to base clinical management to counsel women, with regard to both maternal and neonatal outcomes.
Method: We conducted a retrospective multicentre study of women with established CAD delivering at 16 UK specialised cardiac obstetric clinics. We included pregnancies of 24 weeks' gestation or more, delivered between January 1998 and October 2018. Data were collected on maternal cardiovascular, obstetric and neonatal events.
Results: 79 women who had 92 pregnancies (94 babies including two sets of twins) were identified. 35.9% had body mass index >30% and 24.3% were current smokers. 18/79 (22.8%) had prior diabetes, 27/79 (34.2%) had dyslipidaemia and 21/79 (26.2%) had hypertension. The underlying CAD was due to atherosclerosis in 52/79 (65.8%), spontaneous coronary artery dissection (SCAD) in 11/79 (13.9%), coronary artery spasm in 7/79 (8.9%) and thrombus in 9/79 (11.4%).There were six adverse cardiac events (6.6% event rate), one non-ST elevation myocardial infarction at 23 weeks' gestation, two SCAD recurrences (one at 26 weeks' gestation and one at 9 weeks' postpartum), one symptomatic deterioration in left ventricular function and two women with worsening angina. 14% of women developed pre-eclampsia, 25% delivered preterm and 25% of infants were born small for gestational age.
Conclusion: Women with established CAD have relatively low rates of adverse cardiac events in pregnancy. Rates of adverse obstetric and neonatal events are greater, highlighting the importance of multidisciplinary care.

Gepubliceerd: Heart. 2020;106(5):380-6.
Impact factor: 5.213; Q1

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3. COVID-19 infection during the third trimester of pregnancy: Current clinical dilemmas
Fontanella F, Hannes S, Keating N, Martyn F, Browne I, Briet J, McAuliffe FM, Baalman JH.

Gepubliceerd: Eur J Obstet Gynecol Reprod Biol. 2020;251:268-71.
Impact factor: 1.868; Q3

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4. Reduced morbidity by using LigaSure compared to conventional inguinofemoral lymphadenectomy in vulvar cancer patients: A randomized controlled trial
Pouwer AW, Arts HJ, Koopmans CM, IntHout J, Pijnenborg JMA, de Hullu JA.

Background: Inguinofemoral lymphadenectomy (IFL) is part of the surgical treatment of different malignancies of the genital tract and/or the lower limb including vulvar carcinoma, penile carcinoma and melanoma. IFL is associated with morbidity in up to 85% of the patients. The aims of this MAMBO-IC study (Morbidity And Measurement of the Body) are to study the feasibility of using LigaSure for IFL and to assess the differences in the incidence of short-term complications using LigaSure versus conventional IFL randomized within each individual patient.

Methods: In this multicenter randomized controlled trial (RCT), women diagnosed with squamous cell carcinoma of the vulva with an indication for bilateral IFL were included. It was randomly assigned for which groin the LigaSure was used; the other groin was treated with conventional IFL (sharp/diathermia). We estimated the incidence of ≥1 complication(s) per groin using logistic regression and compared this between the two surgical methods, adjusting for possible confounders.
Results: We included 40 groins of 20 patients. The estimated incidence of ≥1 complication(s) was 29% after LigaSure versus 70% after conventional IFL (risk difference 41% (95% CI 19-62), $p < 0.001$). Patients' reported restriction of daily living activities and maximum pain score were equal for both treatment methods. There were no differences in the surgeon reported workload scores.
Conclusions: This RCT shows that LigaSure for IFL is feasible and associated with significantly less short-term surgical complications compared to conventional IFL. Further studies with a larger sample size are needed to validate our findings. ISRCTN15057626.

Gepubliceerd: Surg Oncol. 2020;35:149-55.
Impact factor: 2.521; Q2

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5. Transvaginal hydrolaparoscopy and laparoscopy
Tros R, van Kessel M, Oosterhuis J, Kuchenbecker W, Bongers M, Mol BW, Koks C.

Research Question: To evaluate the findings of outpatient transvaginal hydrolaparoscopy (THL) in comparison with diagnostic laparoscopy combined with chromopertubation in subfertile women.
Design: In a retrospective study in four large teaching hospitals, all subfertile women who underwent a THL and a conventional laparoscopy as part of their fertility work-up in the period between 2000 and 2011 were studied. Findings at THL were compared with findings at diagnostic and therapeutic laparoscopies. Tubal occlusion, endometriosis and adhesions were defined as abnormalities.
Results: Out of 1119 women, 1103 women underwent THL. A complete evaluation or incomplete but diagnostic procedure could be performed in 989 (89.7%) and 28 (2.5%), respectively. An incomplete non-diagnostic procedure was performed in 11 (1.0%) women. Failure of THL occurred in 75 women (6.8%) and 40 of these women (3.6%) subsequently underwent laparoscopy. Laparoscopy was performed in a total of 126 patients with a median time interval of 7 weeks (interquartile range [IQR] 3-13 weeks). Of 64 patients who successfully underwent both THL and laparoscopy, concordant findings were found in 53 women and discordant results in 11 women, 6 of which were caused by tubal spasm. Sensitivity of THL in detecting abnormalities was 100% and specificity was 22.2%, with a likelihood ratio of 1.29.
Conclusion: THL in an outpatient setting can detect anatomical abnormalities comparable to the more invasive reference standard diagnostic laparoscopy. If THL succeeds, there is no need to add a diagnostic laparoscopy in the work-up.

Gepubliceerd: Reprod Biomed Online. 2020;40(1):105-12.
Impact factor: 3.218; Q1

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6. Perioperative Narcotic Trends in Women Undergoing Minimally Invasive Myomectomy
Tyan P, Klebanoff JS, Smith S, Amdur R, North A, Maassen MS, Moawad GN.

Objective: Evaluate the perioperative narcotic utilization patterns at the time of myomectomy, specifically as they relate to the opioid epidemic. We also aim to evaluate the differences between conventional laparoscopy and robotic surgery in terms of narcotic utilization.
Design: Retrospective cohort study.
Setting: Single academic university hospital.
Patients: Women undergoing minimally invasive myomectomy.
Interventions Laparoscopic or robot-assisted myomectomy.
Measurements And Main Results: We identified 312 minimally invasive myomectomies to be included in the final analysis. For the entire cohort, the mean age (± standard deviation) was 35.7 ± 5.1 years, and the mean body mass index was 28.3 ± 6.3. Of the 312 myomectomies included, 239 (76.6%) were performed using robotic assistance, and the remainder (23.4%) were performed by conventional laparoscopy. A statistically significant inverse relationship was found between year of myomectomy and perioperative narcotic administration ($p < .001$). Yearly morphine milligram equivalent (MME) administration decreased significantly for both intraoperative and postoperative administration ($p < .001$). The largest decline for intraoperative MME use was between 2016 and 2017, and for postoperative MME use, it was between 2012 and 2013. There was no statistically significant difference in perioperative narcotic administration between conventional laparoscopy and robot-assisted myomectomy. The time effect for intraoperative ($p < .001$) and postoperative ($p < .001$) narcotic administration remained significant after adjusting for covariates, including mode of surgery, race, insurance, age, and body mass index. None of the background variables assessed were associated with perioperative narcotic administration.
Conclusion: Perioperative narcotic administration for minimally invasive myomectomy has decreased following widespread awareness of the national opioid crisis.

Gepubliceerd: J Minim Invasive Gynecol. 2020;27(6):1383-8.e1.
Impact factor: 3.107; Q1

Totale impact factor: 20.590
Gemiddelde impact factor: 3.432

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 5.086
Gemiddelde impact factor: 2.543

Heelkunde

1. A patient- and assessor-blinded randomized controlled trial of axillary reverse mapping (ARM) in patients with early breast cancer
Beek MA, Gobardhan PD, Klompenhouwer EG, Menke-Pluijmers MB, Steenvoorde P, Merkus JW, Rutten HJ, Voogd AC, Luiten EJ.

Background: Axillary lymph node dissection (ALND) in breast cancer patients is infamous for its accompanying morbidity. Selective preservation of upper extremity lymphatic drainage and accompanying lymph nodes crossing the axillary basin - currently resected during a standard ALND - has been proposed as a valuable surgical refinement.
Methods: Peroperative Axillary Reversed Mapping (ARM) was used for selective preservation of upper extremity lymphatic drainage. A multicentre patient- and assessor-blinded randomized study was performed in clinical node negative, sentinel node positive early breast cancer patients. Patients were randomized to undergo either standard-ALND or ARM-ALND. Primary outcome was the presence of surgery-related lymphedema at six, 12 and 24 months post-operatively. Secondary outcomes included patient reported and objective signs and symptoms of lymphedema, pain, paraesthesia, numbness, loss of shoulder mobility, quality of life and axillary recurrence risk.
Results: No significant differences were found between both groups using the water displacement method with respect to measured lymphedema. ARM-ALND resulted in less reported complaints of lymphedema at six, 12 and 24 months postoperatively ($p < 0.05$). No axillary recurrence was found in both groups.
Conclusions: In contrast to results of volumetric measurement, patient reported outcomes support selective sparing of the upper extremity lymphatic drainage using ARM as valuable surgical refinement in case of ALND in clinically node negative, sentinel node positive early breast cancer. If completion ALND in clinically node negative, sentinel node positive early breast cancer is considered, selective sparing of upper extremity axillary lymphatics by implementing ARM should be carried out in order to reduce morbidity.

Gepubliceerd: Eur J Surg Oncol. 2020;46(1):59-64.
Impact factor: 3.959; Q1

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2. External iliac artery injury following total hip arthroplasty via the direct anterior approach-a case report
Burlage E, Gerbers JG, Geelkerken BRH, Verra WC.

Gepubliceerd: Acta Orthop. 2020;91(4):485-8.
Impact factor: 2.965; Q1

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3. Applying Risk-Based Follow-Up Strategies on the Dutch Breast Cancer Population: Consequences for Care and Costs
Draeger T, Voelkel V, Groothuis-Oudshoorn CGM, Lavric M, Veltman J, Dassen A, Boersma LJ, Witteveen A, Sonke GS, Koffijberg H, Siesling S.

Objectives: An important aim of follow-up after primary breast cancer treatment is early detection of locoregional recurrences (LRR). This study compares 2 personalized follow-up scheme simulations based on LRR risk predictions provided by a time-dependent prognostic model for breast cancer LRR and quantifies their possible follow-up efficiency.
Methods: Surgically treated early patients with breast cancer between 2003 and 2008 were selected from the Netherlands Cancer Registry. The INFLUENCE nomogram was used to estimate the 5-year annual LRR. Applying 2 thresholds, they were defined according to Youden's J-statistic and a predefined follow-up sensitivity of 95%, respectively. These patient's risk estimations served as the basis for scheduling follow-up visits; 2 personalized follow-up schemes were simulated. The number of potentially saved follow-up visits and corresponding cost savings for each follow-up scheme were compared with the current Dutch breast cancer guideline recommendation and the observed utilization of follow-up on a training and testing cohort.
Results: Using LRR risk-predictions for 30 379 Dutch patients with breast cancer from 2003 to 2006 (training cohort), 2 thresholds were calculated. The threshold according to Youden's approach yielded a follow-up sensitivity of 62.5% and a potential saving of 62.1% of follow-up visits and €24.8 million in 5 years. When the threshold corresponding to 95% follow-up sensitivity was used, 17% of follow-up visits and €7 million were saved compared with the guidelines. Similar results were obtained by applying these thresholds to the testing cohort of 11 462 patients from 2007 to 2008. Compared with the observed utilization of follow-up, the potential cost-savings decline moderately.
Conclusions: Personalized follow-up schemes based on the INFLUENCE nomogram's individual risk estimations for breast cancer LRR could decrease the number of follow-up visits if one accepts a limited risk of delayed LRR detection.

Gepubliceerd: Value Health. 2020;23(9):1149-56.
Impact factor: 4.748; Q1

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4. The Dutch nationwide trauma registry: The value of capturing all acute trauma admissions

Driessen MLS, Sturms LM, Bloemers FW, Ten Duis HJ, Edwards MJR, den Hartog D, de Jongh MAC, Leenhouts PA, Poeze M, Schipper IB, Spanjersberg WR, Wendt KW, de Wit RJ, van Zutphen S, Leenen LPH.

Introduction: Twenty years ago, the Dutch trauma care system was reformed by the designating 11 level one Regional trauma centres (RTCs) to organise trauma care. The RTCs set up the Dutch National Trauma Registry (DNTR) to evaluate epidemiology, patient distribution, resource use and quality of care. In this study we describe the DNTR, the incidence and main characteristics of Dutch acutely admitted trauma patients, and evaluate the value of including all acute trauma admissions compared to more stringent criteria applied by the national trauma registries of the United Kingdom and Germany.
Methods: The DNTR includes all injured patients treated at the ED within 48 hours after trauma and consecutively followed by direct admission, transfers to another hospital or death at the ED. DNTR data on admission years 2007-2018 were extracted to describe the maturation of the registry. Data from 2018 was used to describe the incidence rate and patient characteristics. Inclusion criteria of the

Trauma Audit and Research (TARN) and the Deutsche Gesellschaft für Unfallchirurgie (DGU) were applied on 2018 DNTR data.
Results: Since its start in 2007 a total of 865,460 trauma cases have been registered in the DNTR. Hospital participation increased from 64% to 98%. In 2018, a total of 77,529 patients were included, the median age was 64 years, 50% males. Severely injured patients with an ISS≥16, accounted for 6% of all admissions, of which 70% was treated at designated RTCs. Patients with an ISS≤ 15were treated at non-RTCs in 80% of cases. Application of DGU or TARN inclusion criteria, resulted in inclusion of respectively 5% and 32% of the DNTR patients. Particularly children, elderly and patients admitted at non-RTCs are left out. Moreover, 50% of ISS≥16 and 68% of the fatal cases did not meet DGU inclusion criteria
Conclusion: The DNTR has evolved into a comprehensive well-structured nationwide population-based trauma register. With 80,000 inclusions annually, the DNTR has become one of the largest trauma databases in Europe. The registries strength lies in the broad inclusion criteria which enables studies on the burden of injury and the quality and efficiency of the entire trauma care system, encompassing all trauma-receiving hospitals.

Gepubliceerd: Injury. 2020;51(11):2553-9.
Impact factor: 2.106; Q2

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5. Population-based study on practice variation regarding preoperative systemic chemotherapy in patients with colorectal liver metastases and impact on short-term outcomes
Elfrink AKE, Kok NFM, van der Werf LR, Krul MF, Marra E, Wouters M, Verhoef C, Kuhlmann KFD, den Dulk M, Swijnenburg RJ, Te Riele WW, van den Boezem PB, Leclercq WKG, Lips DJ, Nieuwenhuijs VB, Gobardhan PD, Hartgrink HH, Buis CI, Grünhagen DJ, Klaase JM.

Introduction: Definitions regarding resectability and hence indications for preoperative chemotherapy vary. Use of preoperative chemotherapy may influence postoperative outcomes. This study aimed to assess the variation in use of preoperative chemotherapy for CRLM and related postoperative outcomes in the Netherlands. MATERIALS AND
Methods: All patients who underwent liver resection for CRLM in the Netherlands between 2014 and 2018 were included from a national database. Case-mix factors contributing to the use of preoperative chemotherapy, hospital variation and postoperative outcomes were assessed using multivariable logistic regression. Postoperative outcomes were postoperative complicated course (PCC), 30-day morbidity and 30-day mortality.
Results: In total, 4469 patients were included of whom 1314 patients received preoperative chemotherapy and 3155 patients did not. Patients receiving chemotherapy were significantly younger (mean age (+SD) 66.3 (10.4) versus 63.2 (10.2) $p < 0.001$) and had less comorbidity (Charlson scores 2+ (24% versus 29%, $p = 0.010$). Unadjusted hospital variation concerning administration of preoperative chemotherapy ranged between 2% and 55%. After adjusting for case-mix factors, three hospitals administered significantly more preoperative chemotherapy than expected and six administered significantly less preoperative chemotherapy than expected. PCC was 12.1%, 30-day morbidity was 8.8% and 30-day mortality was

1.5%. No association between preoperative chemotherapy and PCC (OR 1.24, 0.98-1.55, p = 0.065), 30-day morbidity (OR 1.05, 0.81-1.39, p = 0.703) or with 30-day mortality (OR 1.22, 0.75-2.09, p = 0.467) was found.
Conclusion: Significant hospital variation in the use of preoperative chemotherapy for CRLM was present in the Netherlands. No association between postoperative outcomes and use of preoperative chemotherapy was found.

Gepubliceerd: Eur J Surg Oncol. 2020;46(9):1742-55.
Impact factor: 3.959; Q1

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6. Preoperative imaging for colorectal liver metastases: a nationwide population-based study
Elfrink AKE, Pool M, van der Werf LR, Marra E, Burgmans MC, Meijerink MR, den Dulk M, van den Boezem PB, Te Riele WW, Patijn GA, Wouters M, Leclercq WKG, Liem MSL, Gobardhan PD, Buis CI, Kuhlmann KFD, Verhoef C, Besselink MG, Grünhagen DJ, Klaase JM, Kok NFM.

Background: In patients with colorectal liver metastases (CRLM) preoperative imaging may include contrast-enhanced (ce) MRI and [(18) Ffluorodeoxyglucose ((18) F-FDG) PET-CT. This study assessed trends and variation between hospitals and oncological networks in the use of preoperative imaging in the Netherlands.
Methods: Data for all patients who underwent liver resection for CRLM in the Netherlands between 2014 and 2018 were retrieved from a nationwide auditing database. Multivariable logistic regression analysis was used to assess use of ceMRI, (18) F-FDG PET-CT and combined ceMRI and (18) F-FDG PET-CT, and trends in preoperative imaging and hospital and oncological network variation.
Results: A total of 4510 patients were included, of whom 1562 had ceMRI, 872 had (18) F-FDG PET-CT, and 1293 had combined ceMRI and (18) F-FDG PET-CT. Use of ceMRI increased over time (from 9·6 to 26·2 per cent; P < 0·001), use of (18) F-FDG PET-CT decreased (from 28·6 to 6·0 per cent; P < 0·001), and use of both ceMRI and (18) F-FDG PET-CT 16·9 per cent) remained stable. Unadjusted variation in the use of ceMRI, (18) F-FDG PET-CT, and combined ceMRI and (18) F-FDG PET-CT ranged from 5·6 to 100 per cent between hospitals. After case-mix correction, hospital and oncological network variation was found for all imaging modalities.
Discussion: Significant variation exists concerning the use of preoperative imaging for CRLM between hospitals and oncological networks in the Netherlands. The use of MRI is increasing, whereas that of (18) F-FDG PET-CT is decreasing.

Gepubliceerd: BJS Open. 2020;4(4):605-21.
Impact factor: nvt; nvt

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7. Editor's Choice - Nationwide Analysis of Patients Undergoing Iliac Artery Aneurysm Repair in the Netherlands
Jalalzadeh H, Indrakusuma R, Koelemay MJW, Balm R, Van den Akker LH, Van den Akker PJ, Akkersdijk GJ, Akkersdijk GP, Akkersdijk WL, van Andringa de Kempenaer MG, Arts CH, Avontuur JA, Baal JG, Bakker OJ, Balm R, Barendregt WB, Bender MH, Bendermacher BL, van den Berg M, Berger P, Beuk RJ, Blankensteijn JD,

Bleker RJ, Bockel JH, Bodegom ME, Bogt KE, Boll AP, Booster MH, Borger van der Burg BL, de Borst GJ, Bos-van Rossum WT, Bosma J, Botman JM, Bouwman LH, Breek JC, Brehm V, Brinckman MJ, van den Broek TH, Brom HL, de Bruijn MT, de Bruin JL, Brummel P, van Brussel JP, Buijk SE, Buimer MG, Burger DH, Buscher HC, den Butter G, Cancrinus E, Castenmiller PH, Cazander G, Coveliers HM, Cuypers PH, Daemen JH, Dawson I, Derom AF, Dijkema AR, Diks J, Dinkelman MK, Dirven M, Dolmans DE, van Doorn RC, van Dortmont LM, van der Eb MM, Eefting D, van Eijck GJ, Elshof JW, Elsman BH, van der Elst A, van Engeland MI, van Eps RG, Faber MJ, de Fijter WM, Fioole B, Fritschy WM, Geelkerken RH, van Gent WB, Glade GJ, Govaert B, Groenendijk RP, de Groot HG, van den Haak RF, de Haan EF, Hajer GF, Hamming JF, van Hattum ES, Hazenberg CE, Hedeman Joosten PP, Helleman JN, van der Hem LG, Hendriks JM, van Herwaarden JA, Heyligers JM, Hinnen JW, Hissink RJ, Ho GH, den Hoed PT, Hoedt MT, van Hoek F, Hoencamp R, Hoffmann WH, Hoksbergen AW, Hollander EJ, Huisman LC, Hulsebos RG, Huntjens KM, Idu MM, Jacobs MJ, van der Jagt MF, Jansbeken JR, Janssen RJ, Jiang HH, de Jong SC, Jongkind V, Kapma MR, Keller BP, Khodadade Jahrome A, Kievit JK, Klemm PL, Klinkert P, Knippenberg B, Koedam NA, Koelemay MJ, Kolkert JL, Koning GG, Koning OH, Krasznai AG, Krol RM, Kropman RH, Kruse RR, van der Laan L, van der Laan MJ, van Laanen JH, Lardenoye JH, Lawson JA, Legemate DA, Leijdekkers VJ, Lemson MS, Lensvelt MM, Lijkwan MA, Lind RC, van der Linden FT, Liqui Lung PF, Loos MJ, Loubert MC, Mahmoud DE, Manshanden CG, Mattens EC, Meerwaldt R, Mees BM, Metz R, Minnee RC, de Mol van Otterloo JC, Moll FL, Montauban van Swijndregt YC, Morak MJ, van de Mortel RH, Mulder W, Nagesser SK, Naves CC, Nederhoed JH, Nevenzel-Putters AM, de Nie AJ, Nieuwenhuis DH, Nieuwenhuizen J, van Nieuwenhuizen RC, Nio D, Oomen AP, Oranen BI, Oskam J, Palamba HW, Peppelenbosch AG, van Petersen AS, Peterson TF, Petri BJ, Pierie ME, Ploeg AJ, Pol RA, Ponfoort ED, Poyck PP, Prent A, Ten Raa S, Raymakers JT, Reichart M, Reichmann BL, Reijnen MM, Rijbroek A, van Rijn MJ, de Roo RA, Rouwet EV, Rupert CG, Saleem BR, van Sambeek MR, Samyn MG, van 't Sant HP, van Schaik J, van Schaik PM, Scharn DM, Scheltinga MR, Schepers A, Schlejen PM, Schlosser FJ, Schol FP, Schouten O, Schreinemacher MH, Schreve MA, Schurink GW, Sikkink CJ, Siroen MP, Te Slaa A, Smeets HJ, Smeets L, de Smet AA, de Smit P, Smit PC, Smits TM, Snoeijs MG, Sondakh AO, van der Steenhoven TJ, van Sterkenburg SM, Stigter DA, Stigter H, Strating RP, Stultiëns GN, Sybrandy JE, Teijink JA, Telgenkamp BJ, Testroote MJ, The RM, Thijsse WJ, Tielliu IF, van Tongeren RB, Toorop RJ, Tordoir JH, Tournoij E, Truijers M, Türkcan K, Tutein Nolthenius RP, Ünlü Ç, Vafi AA, Vahl AC, Veen EJ, Veger HT, Veldman MG, Verhagen HJ, Verhoeven BA, Vermeulen CF, Vermeulen EG, Vierhout BP, Visser MJ, van der Vliet JA, Vlijmen-van Keulen CJ, Voesten HG, Voorhoeve R, Vos AW, de Vos B, Vos GA, Vriens BH, Vriens PW, de Vries AC, de Vries JP, de Vries M, van der Waal C, Waasdorp EJ, Wallis de Vries BM, van Walraven LA, van Wanroij JL, Warlé MC, van Weel V, van Well AM, Welten GM, Welten RJ, Wever JJ, Wiersema AM, Wikkeling OR, Willaert WI, Wille J, Willems MC, Willigendael EM, Wisselink W, Witte ME, Wittens CH, Wolf-de Jonge IC, Yazar O, Zeebregts CJ, van Zeeland ML.

Objective: The new 2019 guideline of the European Society for Vascular Surgery (ESVS) recommends consideration for elective iliac artery aneurysm (eIAA) repair when the iliac diameter exceeds 3.5 cm, as opposed to 3.0 cm previously. The current study assessed diameters at time of eIAA repair and ruptured IAA (rIAA)

repair and compared clinical outcomes after open surgical repair (OSR) and endovascular aneurysm repair (EVAR).
Methods: This retrospective observational study used the nationwide Dutch Surgical Aneurysm Audit (DSAA) registry that includes all patients who undergo aorto-iliac aneurysm repair in the Netherlands. All patients who underwent primary IAA repair between 1 January 2014 and 1 January 2018 were included. Diameters at time of eIAA and rIAA repair were compared in a descriptive fashion. The anatomical location of the IAA was not registered in the registry. Patient characteristics and outcomes of OSR and EVAR were compared with appropriate statistical tests.
Results: The DSAA registry comprised 974 patients who underwent IAA repair. A total of 851 patients were included after exclusion of patients undergoing revision surgery and patients with missing essential variables. eIAA repair was carried out in 713 patients, rIAA repair in 102, and symptomatic IAA repair in 36. OSR was performed in 205, EVAR in 618, and hybrid repairs and conversions in 28. The median maximum IAA diameter at the time of eIAA and rIAA repair was 43 (IQR 38-50) mm and 68 (IQR 58-85) mm, respectively. Mortality was 1.3% (95% CI 0.7-2.4) after eIAA repair and 25.5% (95% CI 18.0-34.7) after rIAA repair. Mortality was not significantly different between the OSR and EVAR subgroups. Elective OSR was associated with significantly more complications than EVAR (intra-operative: 9.8% vs. 3.6%, post-operative: 34.0% vs. 13.8%, respectively).
Conclusion: In the Netherlands, most eIAA repairs are performed at diameters larger than recommended by the ESVS guideline. These findings appear to support the recent increase in the threshold diameter for eIAA repair.

Gepubliceerd: Eur J Vasc Endovasc Surg. 2020;60(1):49-55.
Impact factor: 5.328; Q1

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8. Outcomes After Minimally-invasive Versus Open Pancreatoduodenectomy: A Pan-European Propensity Score Matched Study
Klompmaker S, van Hilst J, Wellner UF, Busch OR, Coratti A, D'Hondt M, Dokmak S, Festen S, Kerem M, Khatkov I, Lips DJ, Lombardo C, Luyer M, Manzoni A, Molenaar IQ, Rosso E, Saint-Marc O, Vansteenkiste F, Wittel UA, Bonsing B, Groot Koerkamp B, Abu Hilal M, Fuks D, Poves I, Keck T, Boggi U, Besselink MG.

Objective: To assess short-term outcomes after minimally invasive (laparoscopic, robot-assisted, and hybrid) pancreatoduodenectomy (MIPD) versus open pancreatoduodenectomy (OPD) among European centers.
Background: Current evidence on MIPD is based on national registries or single expert centers. International, matched studies comparing outcomes for MIPD and OPD are lacking.
Methods: Retrospective propensity score matched study comparing MIPD in 14 centers (7 countries) performing ≥10 MIPDs annually (2012-2017) versus OPD in 53 German/Dutch surgical registry centers performing ≥10 OPDs annually (2014-2017). Primary outcome was 30-day major morbidity (Clavien-Dindo ≥3).
Results: Of 4220 patients, 729/730 MIPDs (412 laparoscopic, 184 robot-assisted, and 130 hybrid) were matched to 729 OPDs. Median annual case-volume was 19 MIPDs (interquartile range, IQR 13-22), including the first MIPDs performed in 10/14 centers, and 31 OPDs (IQR 21-38). Major morbidity (28% vs 30%, P = 0.526),

mortality (4.0% vs 3.3%, P = 0.576), percutaneous drainage (12% vs 12%, P = 0.809), reoperation (11% vs 13%, P = 0.329), and hospital stay (mean 17 vs 17 days, P > 0.99) were comparable between MIPD and OPD. Grade-B/C postoperative pancreatic fistula (POPF) (23% vs 13%, P < 0.001) occurred more frequently after MIPD. Single-row pancreatojejunostomy was associated with POPF in MIPD (odds ratio, OR 2.95, P < 0.001), but not in OPD. Laparoscopic, robot-assisted, and hybrid MIPD had comparable major morbidity (27% vs 27% vs 35%), POPF (24% vs 19% vs 25%), and mortality (2.9% vs 5.2% vs 5.4%), with fewer conversions in robot-assisted- versus laparoscopic MIPD (5% vs 26%, P < 0.001).
Conclusions: In the early experience of 14 European centers performing ≥10 MIPDs annually, no differences were found in major morbidity, mortality, and hospital stay between MIPD and OPD. The high rates of POPF and conversion, and the lack of superior outcomes (i.e., hospital stay, morbidity) could indicate that more experience and higher annual MIPD volumes are needed.

Gepubliceerd: Ann Surg. 2020;271(2):356-63.
Impact factor: 10.130; Q1

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9. Electrocardiography-gated computed tomography angiography analysis of cardiac pulsatility-induced motion and deformation after endovascular aneurysm sealing with chimney grafts
Koenrades MA, Donselaar EJ, van Erp M, Loonen TGJ, van Lochem P, Klein A, Geelkerken RH, Reijnen M.

Objective: To evaluate the proximal stability of the chimney endovascular aneurysm sealing configuration (chEVAS) during the cardiac cycle by investigating the cardiac pulsatility-induced movement and deformation.
Methods: We retrospectively analyzed postoperative electrocardiogram-gated computed tomography angiography scans of 11 chEVAS cases (9 primary chEVAS plus 2 chEVAS-in-chEVAS). ChEVAS procedures were conducted between September 2013 and June 2016. Motion and deformation of the EVAS stents, the chimney grafts, and the stented branch vessels were evaluated during the cardiac cycle using an established combination of image registration and segmentation techniques.
Results: Electrocardiogram-gated computed tomography angiography scans of 11 chEVAS configurations including 22 EVAS stents and 20 chimney grafts were analyzed. The three-dimensional displacement was at most 1.7 mm for both the EVAS stents and the chimney grafts. The maximum change in distance between components was no more than 0.4 mm and did not differ between EVAS-to-EVAS stent and EVAS stent-to-chimney stent (0.2 ± 0.1 mm vs 0.2 ± 0.1 mm; P = .823). The mean change in chimney deflection angle was 1.2 ± 0.7°; the maximum change was greatest for the superior mesenteric artery (SMA) (2.6°). The EVAS stent-to-chimney angles for the left renal artery, right renal artery, and SMA varied on average by 0.7 ± 0.3° (range, 0.4°-1.3°), 1.0 ± 0.3° (range, 0.5°-1.7°), and 0.8 ± 0.4° (range, 0.3°-1.3°), respectively, during the cardiac cycle. The end-stent angles for the left renal artery, right renal artery, and SMA varied on average by 1.7 ± 0.9° (range, 0.5°-3.3°), 1.9 ± 0.8° (range, 0.7°-3.3°), and 1.3 ± 0.4° (range, 0.7°-1.6°), respectively, during the cardiac cycle. Overall, the end-stent angles varied on average by 1.7 ± 0.8° (range, 0.5°-3.3°).

Conclusions: The chEVAS configuration proved to be stable during the cardiac cycle, as demonstrated by minimal cyclical changes in distance between device components and angulation between the EVAS stents and the chimney grafts. The limited deflection angles of the chimney grafts decrease the risk of bending fatigue, but the more apparent change in end-stent angle distal to the chimney graft may raise concerns regarding late branch occlusion or stenosis.

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Impact factor: 3.405; Q1

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10. A hybrid treatment modality of a subtrochanteric femoral fracture in a patient with osteoporosis due to a renal Fanconi syndrome: a case report
Lange SF, Schrooten TKJ, de Wit RJ, de Groot R.

A 24-year-old male with an idiopathic renal Fanconi syndrome presented to our ER after a low-energetic fall. Conventional imaging revealed a right subtrochanteric femoral fracture, severely decreased bone quality and cannulated collum femoris screws on the contralateral side. Regular plate-screw osteosynthesis or cephalomedullary implantation was deemed insufficient, due to a high iatrogenic and periprosthetic fracture probability. The decision was made to perform a plate-screw osteosynthesis combined with an intramedullary polymer bone enhancement (IlluminOss), to minimize this risk. No complications occurred perioperatively. The patient was able to walk independently two months postoperatively. This case shows that use of polymer implant as an enhancement of osteosynthesis in repair of fractures in the Fanconi syndrome is a safe and possible useful treatment method.

Gepubliceerd: J Surg Case Rep. 2020;2020(8):rjaa130.
Impact factor: nvt; nvt

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11. Are computed tomography-based measures of specific abdominal muscle groups predictive of adverse outcomes in older cancer patients?
Looijaard S, Maier AB, Voskuilen AF, Van Zanten T, Bouman DE, Klaase JM, Meskers CGM.

Purpose: It is unknown whether computed tomography (CT)-based total abdominal muscle measures are representative of specific abdominal muscle groups and whether analysis of specific abdominal muscle groups are predictive of the risk of adverse outcomes in older cancer patients.
Methods: Retrospective single-center cohort study in elective colon cancer patients aged ≥65 years. CT-based skeletal muscle (SM) surface area, muscle density and intermuscular adipose tissue (IMAT) surface area were determined for rectus abdominis; external- and internal oblique and transversus abdominis (lateral muscles); psoas; and erector spinae and quadratus lumborum (back muscles). Outcomes were defined as severe postoperative complications (Clavien-Dindo score >2) and long-term survival (median follow-up 5.2 years).
Results: 254 older colon cancer patients were included (median 73.6 years, 62.2% males). Rectus abdominis showed the lowest SM surface area and muscle density and the back muscles showed the highest IMAT surface area. Psoas muscle density,

and lateral muscle density and percentage IMAT were associated with severe postoperative complications independent of gender, age and cancer stage.
Conclusions: CT-based total abdominal muscle quantity and quality do not represent the heterogeneity that exists between specific muscle groups. The potential added value of analysis of specific muscle groups in predicting adverse outcomes in older (colon) cancer patients should be further addressed in prospective studies.

Gepubliceerd: Heliyon. 2020;6(11):e05437.
Impact factor: nvt; nvt

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12. Computed Tomography-Based Body Composition Is Not Consistently Associated with Outcome in Older Patients with Colorectal Cancer
Looijaard S, Meskers CGM, Slee-Valentijn MS, Bouman DE, Wymenga ANM, Klaase JM, Maier AB.

Background: Current literature is inconsistent in the associations between computed tomography (CT)-based body composition measures and adverse outcomes in older patients with colorectal cancer (CRC). Moreover, the associations with consecutive treatment modalities have not been studied. This study compared the associations of CT-based body composition measures with surgery- and chemotherapy-related complications and survival in older patients with CRC. MATERIALS AND
Methods: A retrospective single-center cohort study was conducted in patients with CRC aged ≥65 years who underwent elective surgery between 2010 and 2014. Gender-specific standardized scores of preoperative CT-based skeletal muscle (SM), muscle density, intermuscular adipose tissue (IMAT), visceral adipose tissue (VAT), subcutaneous adipose tissue, IMAT percentage, SM/VAT, and body mass index (BMI) were tested for their associations with severe postoperative complications, prolonged length of stay (LOS), readmission, and dose-limiting toxicity using logistic regression and 1-year and long-term survival (range 3.7-6.6 years) using Cox regression. Bonferroni correction was applied to account for multiple testing.
Results: The study population consisted of 378 patients with CRC with a median age of 73.4 (interquartile range 69.5-78.4) years. Severe postoperative complications occurred in 13.0%, and 39.4% of patients died during follow-up. Dose-limiting toxicity occurred in 77.4% of patients receiving chemotherapy (n = 53). SM, muscle density, VAT, SM/VAT, and BMI were associated with surgery-related complications, and muscle density, IMAT, IMAT percentage, and SM/VAT were associated with long-term survival. After Bonferroni correction, no CT-based body composition measure was significantly associated with adverse outcomes. Higher BMI was associated with prolonged LOS.
Conclusion: The associations between CT-based body composition measures and adverse outcomes of consecutive treatment modalities in older patients with CRC were not consistent or statistically significant. IMPLICATIONS FOR PRACTICE: Computed tomography (CT)-based body composition, including muscle mass, muscle density, and intermuscular, visceral, and subcutaneous adipose tissue, showed inconsistent and nonsignificant associations with surgery-related complications, dose-limiting toxicity, and overall survival in older adults with colorectal cancer. This study underscores the need to verify whether CT-based body composition measures are worth implementing in clinical practice.

Gepubliceerd: Oncologist. 2020;25(3):e492-e501.
Impact factor: 5.025; Q2

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13. Impact of nationwide enhanced implementation of best practices in pancreatic cancer care (PACAP-1): a multicenter stepped-wedge cluster randomized controlled trial

Mackay TM, Smits FJ, Latenstein AEJ, Bogte A, Bonsing BA, Bos H, Bosscha K, Brosens LAA, Hol L, Busch ORC, Creemers GJ, Curvers WL, den Dulk M, van Dieren S, van Driel L, Festen S, van Geenen EJM, van der Geest LG, de Groot DJA, de Groot JWB, Haj Mohammad N, Haberkorn BCM, Haver JT, van der Harst E, Hemmink GJM, de Hingh IH, Hoge C, Homs MYV, van Huijgevoort NC, Jacobs M, Kerver ED, Liem MSL, Los M, Lubbinge H, Luelmo SAC, de Meijer VE, Mekenkamp L, Molenaar IQ, van Oijen MGH, Patijn GA, Quispel R, van Rijssen LB, Römkens TEH, van Santvoort HC, Schreinemakers JMJ, Schut H, Seerden T, Stommel MWJ, Ten Tije AJ, Venneman NG, Verdonk RC, Verheij J, van Vilsteren FGI, de Vos-Geelen J, Vulink A, Wientjes C, Wit F, Wessels FJ, Zonderhuis B, van Werkhoven CH, van Hooft JE, van Eijck CHJ, Wilmink JW, van Laarhoven HWM, Besselink MG.

Background: Pancreatic cancer has a very poor prognosis. Best practices for the use of chemotherapy, enzyme replacement therapy, and biliary drainage have been identified but their implementation in daily clinical practice is often suboptimal. We hypothesized that a nationwide program to enhance implementation of these best practices in pancreatic cancer care would improve survival and quality of life.
Methods/Design: PACAP-1 is a nationwide multicenter stepped-wedge cluster randomized controlled superiority trial. In a per-center stepwise and randomized manner, best practices in pancreatic cancer care regarding the use of (neo)adjuvant and palliative chemotherapy, pancreatic enzyme replacement therapy, and metal biliary stents are implemented in all 17 Dutch pancreatic centers and their regional referral networks during a 6-week initiation period. Per pancreatic center, one multidisciplinary team functions as reference for the other centers in the network. Key best practices were identified from the literature, 3 years of data from existing nationwide registries within the Dutch Pancreatic Cancer Project (PACAP), and national expert meetings. The best practices follow the Dutch guideline on pancreatic cancer and the current state of the literature, and can be executed within daily clinical practice. The implementation process includes monitoring, return visits, and provider feedback in combination with education and reminders. Patient outcomes and compliance are monitored within the PACAP registries. Primary outcome is 1-year overall survival (for all disease stages). Secondary outcomes include quality of life, 3- and 5-year overall survival, and guideline compliance. An improvement of 10% in 1-year overall survival is considered clinically relevant. A 25-month study duration was chosen, which provides 80% statistical power for a mortality reduction of 10.0% in the 17 pancreatic cancer centers, with a required sample size of 2142 patients, corresponding to a 6.6% mortality reduction and 4769 patients nationwide.
Discussion: The PACAP-1 trial is designed to evaluate whether a nationwide program for enhanced implementation of best practices in pancreatic cancer care can improve 1-year overall survival and quality of life.
Trial registration: ClinicalTrials.gov, NCT03513705. Trial opened for accrual on 22th May 2018.

Gepubliceerd: Trials. 2020;21(1):334.
Impact factor: 1.883; Q3

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14. The risk of not receiving adjuvant chemotherapy after resection of pancreatic ductal adenocarcinoma: a nationwide analysis
Mackay TM, Smits FJ, Roos D, Bonsing BA, Bosscha K, Busch OR, Creemers GJ, van Dam RM, van Eijck CHJ, Gerhards MF, de Groot JWB, Groot Koerkamp B, Haj Mohammad N, van der Harst E, de Hingh I, Homs MYV, Kazemier G, Liem MSL, de Meijer VE, Molenaar IQ, Nieuwenhuijs VB, van Santvoort HC, van der Schelling GP, Stommel MWJ, Ten Tije AJ, de Vos-Geelen J, Wit F, Wilmink JW, van Laarhoven HWM, Besselink MG.

Background: The relation between type of postoperative complication and not receiving chemotherapy after resection of pancreatic ductal adenocarcinoma (PDAC) is unclear. The aim was to investigate which patient factors and postoperative complications were associated with not receiving adjuvant chemotherapy.
Methods: Patients who underwent resection (2014-2017) for PDAC were identified from the nationwide mandatory Dutch Pancreatic Cancer Audit. The association between patient-, tumor-, center-, treatment characteristics, and the risk of not receiving adjuvant chemotherapy was analyzed with multivariable logistic regression.
Results: Overall, of 1306 patients, 24% (n = 312) developed postoperative Clavien Dindo ≥3 complications. In-hospital mortality was 3.5% (n = 46). Some 433 patients (33%) did not receive adjuvant chemotherapy. Independent predictors (all $p < 0.050$) for not receiving adjuvant chemotherapy were older age (odds ratio (OR) 0.96), higher ECOG performance status (OR 0.57), postoperative complications (OR 0.32), especially grade B/C pancreatic fistula (OR 0.51) and post-pancreatectomy hemorrhage (OR 0.36), poor tumor differentiation grade (OR 0.62), and annual center volume of <40 pancreatoduodenectomies (OR 0.51).
Conclusions: This study demonstrated that a third of patients do not receive chemotherapy after resection of PDAC. Next to higher age, worse performance status and lower annual surgical volume, this is mostly related to surgical complications, especially postoperative pancreatic fistula and post-pancreatectomy hemorrhage.

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Impact factor: 3.401; Q1

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15. Axillary metastases after port site recurrences of gallbladder carcinoma: a case report
Nijhuis J, Bosscher MRF, Liem MSL.

Background: Incidental gallbladder carcinoma is often discovered after elective laparoscopic cholecystectomy for cholecystitis or cholecystolithiasis. Port site recurrences may occur. Patients with port site metastases of gallbladder carcinoma have a poor prognosis.
Case Presentation: A 61-year-old man underwent an elective laparoscopic cholecystectomy because of cholecystitis and gallstones. Pathology revealed a gallbladder carcinoma. After referral to a tertiary center, radical re-resection followed. Three years later, an epigastric port site recurrence emerged, partially fixed to the

xiphoid process. A wide abdominal wall resection was performed, including part of the xiphoid process. Follow-up was continued with periodical imaging and standard blood work. Three years after resection of this port site metastasis, the patient presented with an occasionally painful mass in the left axilla. Pathology revealed the presence of an adenocarcinoma, most likely arising from the prior gallbladder carcinoma. Given the extensive dissemination and limited symptoms in the axillary node, we decided against a surgical intervention, instead of adopting a wait-and-see policy. Disease progression occurred within 1 year, and the patient was treated with palliative radiotherapy, followed by palliative chemotherapy. The patient died of metastatic disease approximately 6.5 years after the initial cholecystectomy.
Conclusions: Port site recurrences of (incidental) gallbladder carcinoma occur after laparoscopic cholecystectomy, despite preventive perioperative measures. Patients with port site recurrences can develop axillary lymph node metastases, similar to other truncal malignancies. Surgical interventions should be limited.

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Impact factor: 1.963; Q2

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16. Volume-outcome relationship of liver surgery: a nationwide analysis
Olthof PB, Elfrink AKE, Marra E, Belt EJT, van den Boezem PB, Bosscha K, Consten ECJ, den Dulk M, Gobardhan PD, Hagendoorn J, van Heek TNT, JNM IJ, Klaase JM, Kuhlmann KFD, Leclercq WKG, Liem MSL, Manusama ER, Marsman HA, Mieog JSD, Oosterling SJ, Patijn GA, Te Riele W, Swijnenburg RJ, Torrenga H, van Duijvendijk P, Vermaas M, Kok NFM, Grünhagen DJ.

Background: Evidence for an association between hospital volume and outcomes for liver surgery is abundant. The current Dutch guideline requires a minimum volume of 20 annual procedures per centre. The aim of this study was to investigate the association between hospital volume and postoperative outcomes using data from the nationwide Dutch Hepato Biliary Audit.
Methods: This was a nationwide study in the Netherlands. All liver resections reported in the Dutch Hepato Biliary Audit between 2014 and 2017 were included. Annual centre volume was calculated and classified in categories of 20 procedures per year. Main outcomes were major morbidity (Clavien-Dindo grade IIIA or higher) and 30-day or in-hospital mortality.
Results: A total of 5590 liver resections were done across 34 centres with a median annual centre volume of 35 (i.q.r. 20-69) procedures. Overall major morbidity and mortality rates were 11·2 and 2·0 per cent respectively. The mortality rate was 1·9 per cent after resection for colorectal liver metastases (CRLMs), 1·2 per cent for non-CRLMs, 0·4 per cent for benign tumours, 4·9 per cent for hepatocellular carcinoma and 10·3 per cent for biliary tumours. Higher-volume centres performed more major liver resections, and more resections for hepatocellular carcinoma and biliary cancer. There was no association between hospital volume and either major morbidity or mortality in multivariable analysis, after adjustment for known risk factors for adverse events.
Conclusion: Hospital volume and postoperative outcomes were not associated.

Gepubliceerd: Br J Surg. 2020;107(7):917-26.
Impact factor: 5.676; Q1

17. A Comparison of Quality of Life in Elderly Patients with Intermittent Claudication and Chronic Limb-Threatening Ischemia
Roijers JP, van den Houten MM, Hopmans NJ, Vriens P, Willigendael EM, Lodder P, de Vries J, Teijink JA, van der Laan L.

Background: Intermittent claudication (IC) and chronic limb-threatening ischemia (CLTI) are both associated with a decreased health status and possibly quality of life (QOL). A better understanding of the differences in QOL between patients with IC and CLTI could be of additional value in shared decision-making. The aim of this study was to compare the QOL at baseline between patients with IC and patients with CLTI.
Methods: The study population was based on 2 study cohorts, 1 cohort consisted of patients with IC (ELECT registry) and the other cohort of patients with CLTI (KOP-study). Patients with an age of ≥70 years were included. QOL at baseline was measured by the WHOQOL-BREF questionnaire. Nonresponders were excluded from data analyses. Student's t-tests and analysis of covariance (ANCOVA) analyses were used to compare QOL between the 2 groups. Outcomes of the ANCOVA analyses were expressed as estimated marginal means.
Results: In total, 308 patients were included, 115 patients with IC and 193 patients with CLTI. Patients with CLTI were older (median age 80 years vs. 75 years, $P < 0.001$) and had more comorbidities. Patients with IC had a statistically significant higher QOL regarding physical health (mean 13.7 [standard deviation (SD) 2.3] vs. 10.8 [SD 2.8], $P < 0.001$), psychological health (mean 15.3 [SD 2.1] vs. 14.1 [SD 2.4], $P < 0.001$), environment (mean 16.3 [SD 2.4] vs. 15.5 [SD 2.0], $P < 0.002$), and the overall domain (mean 3.5 [SD 0.7] vs. 3.1 [SD 0.9], $P < 0.001$). After correcting for the confounding effect of age and sex, patients with IC still had a statistically significant higher QOL in the physical, psychological, environment, and overall domain.
Conclusions: Patients with IC had a significantly higher QOL in the physical, psychological, environment, and overall domains of the WHOQOL-BREF questionnaire compared with patients with CLTI. This underlines the importance of strategies that reduce disease progression as disease progression is associated with a decrease in QOL.

Gepubliceerd: Ann Vasc Surg. 2020;69:285-91.
Impact factor: 1.125; Q4

18. Geometrical changes in Anaconda endograft limbs after endovascular aneurysm repair: A potential predictor for limb occlusion
Simmering JA, Geelkerken RH, Slump CH, Koenrades MA.

The emergence of limb occlusion after endovascular aneurysm repair may be related to the conformational changes between the endograft structure and the patient's anatomy. This study analyzed detailed geometric changes of Anaconda endograft (Terumo Aortic, Inchinnan, Scotland, UK) limbs during the cardiac cycle-based computed tomography on serial imaging after graft implantation. Fifteen patients (mean age 72.8 ± 3.7 years; 14 men) underwent postoperative electrocardiogram-gated computed tomography scans according to a prospective study design between April 2014 and May 2017. Changes in curvature, length of the limbs, and distances

between successive stent rings (inter-ring distance) of the endograft limbs during a 2-year follow-up period were quantified using meticulous image processing methods involving image registration, centerline extraction, and model-based stent-ring segmentation. From discharge to 24 months, mean curvature increased significantly by 9.6 m(-1) (standard deviation [SD], 11.1 m(-1); 95% confidence interval [CI], 3.4 to 15.8 m(-1); P = .002) for the right limbs and by 6.1 m(-1) (SD 9.4 m(-1); 95% CI, 0.8 to 11.5 m(-1); P = .21) for the left limbs. The length of the right limbs decreased significantly, by 9.5 mm (SD 7.6 mm; 95% CI, 3.5 to 15.6 mm; P = .002); the length of the left limbs decreased by 10.1 mm (SD 5.1 mm; 95% CI, 5.9 to 14.2 mm; P < .001). The minimal inter-ring distance decreased by 0.36 mm (SD 0.26 mm; 95% CI, 0.17 to 0.55 mm; P < .001) for the right limbs and 0.35 mm (SD 0.19 mm; 95% CI, 0.21 to 0.49 mm; P < .001) for the left limbs. Cardiac pulsatility-induced changes in curvature, limb length, and inter-ring distance were negligible (2%, 0.3% and 0.3%, respectively). Changes in the geometry of the Anaconda endograft limbs after endovascular aortic aneurysm repair were observed during a 2-year follow-up manifest as an increase in curvature, shortening of the stent-graft limbs, and a corresponding decrease in inter-ring distance. These stent-graft conformational changes could result in inward folding of the graft fabric, which may relate to the emergence of limb occlusion. Further investigation of these metrics in a larger cohort involving patients with and without occlusions may allow determination of their predictive value.

Gepubliceerd: Semin Vasc Surg. 2020;32(3-4):94-105.
Impact factor: 1.889; Q3

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19. Care after pancreatic resection according to an algorithm for early detection and minimally invasive management of pancreatic fistula versus current practice (PORSCH-trial): design and rationale of a nationwide stepped-wedge cluster-randomized trial

Smits FJ, Henry AC, van Eijck CH, Besselink MG, Busch OR, Arntz M, Bollen TL, van Delden OM, van den Heuvel D, van der Leij C, van Lienden KP, Moelker A, Bonsing BA, Borel Rinkes IHM, Bosscha K, van Dam RM, Festen S, Groot Koerkamp B, van der Harst E, de Hingh IH, Kazemier G, Liem M, van der Kolk BM, de Meijer VE, Patijn GA, Roos D, Schreinemakers JM, Wit F, van Werkhoven CH, Molenaar IQ, van Santvoort HC.

Background: Pancreatic resection is a major abdominal operation with 50% risk of postoperative complications. A common complication is pancreatic fistula, which may have severe clinical consequences such as postoperative bleeding, organ failure and death. The objective of this study is to investigate whether implementation of an algorithm for early detection and minimally invasive management of pancreatic fistula may improve outcomes after pancreatic resection.
Methods: This is a nationwide stepped-wedge, cluster-randomized, superiority trial, designed in adherence to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. During a period of 22 months, all Dutch centers performing pancreatic surgery will cross over in a randomized order from current practice to best practice according to the algorithm. This evidence-based and consensus-based algorithm will provide daily multilevel advice on the management of patients after pancreatic resection (i.e., indication for abdominal imaging, antibiotic treatment,

percutaneous drainage and removal of abdominal drains). The algorithm is designed to aid early detection and minimally invasive step-up management of postoperative pancreatic fistula. Outcomes of current practice will be compared with outcomes after implementation of the algorithm. The primary outcome is a composite of major complications (i.e., post-pancreatectomy bleeding, new-onset organ failure and death) and will be measured in a sample size of at least 1600 patients undergoing pancreatic resection. Secondary endpoints include the individual components of the primary endpoint and other clinical outcomes, healthcare resource utilization and costs analysis. Follow up will be up to 90 days after pancreatic resection.
Discussion: It is hypothesized that a structured nationwide implementation of a dedicated algorithm for early detection and minimally invasive step-up management of postoperative pancreatic fistula will reduce the risk of major complications and death after pancreatic resection, as compared to current practice.
Trial registration: Netherlands Trial Register: NL 6671. Registered on 16 December 2017.

Gepubliceerd: Trials. 2020;21(1):389.
Impact factor: 1.883; Q3

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20. European guidelines on chronic mesenteric ischaemia - joint United European Gastroenterology, European Association for Gastroenterology, Endoscopy and Nutrition, European Society of Gastrointestinal and Abdominal Radiology, Netherlands Association of Hepatogastroenterologists, Hellenic Society of Gastroenterology, Cardiovascular and Interventional Radiological Society of Europe, and Dutch Mesenteric Ischemia Study group clinical guidelines on the diagnosis and treatment of patients with chronic mesenteric ischaemia
Terlouw LG, Moelker A, Abrahamsen J, Acosta S, Bakker OJ, Baumgartner I, Boyer L, Corcos O, van Dijk LJ, Duran M, Geelkerken RH, Illuminati G, Jackson RW, Kärkkäinen JM, Kolkman JJ, Lönn L, Mazzei MA, Nuzzo A, Pecoraro F, Raupach J, Verhagen HJ, Zech CJ, van Noord D, Bruno MJ.

Chronic mesenteric ischaemia is a severe and incapacitating disease, causing complaints of post-prandial pain, fear of eating and weight loss. Even though chronic mesenteric ischaemia may progress to acute mesenteric ischaemia, chronic mesenteric ischaemia remains an underappreciated and undertreated disease entity. Probable explanations are the lack of knowledge and awareness among physicians and the lack of a gold standard diagnostic test. The underappreciation of this disease results in diagnostic delays, underdiagnosis and undertreating of patients with chronic mesenteric ischaemia, potentially resulting in fatal acute mesenteric ischaemia. This guideline provides a comprehensive overview and repository of the current evidence and multidisciplinary expert agreement on pertinent issues regarding diagnosis and treatment, and provides guidance in the multidisciplinary field of chronic mesenteric ischaemia.

Gepubliceerd: United European Gastroenterol J. 2020;8(4):371-95.
Impact factor: 3.549; Q2

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21. The Incidence of Chronic Mesenteric Ischemia in the Well-Defined Region of a Dutch Mesenteric Ischemia Expert Center
Terlouw LG, Verbeten M, van Noord D, Brusse-Keizer M, Beumer RR, Geelkerken RH, Bruno MJ, Kolkman JJ.

Introduction: This study aimed to determine the incidence of chronic mesenteric ischemia (CMI) and to examine the influence of the etiological cause, location, and severity of a mesenteric artery stenosis on the probability of having CMI.
Methods: A prospective database, containing the details of all patients with suspected CMI referred to a renowned CMI expert center, was used. Patients residing within the expert centers' well-defined region, between January 2014 and October 2019, were included. CMI was diagnosed when patients experienced sustained symptom improvement after treatment.
Results: This study included 358 patients, 75 had a ≥50% atherosclerotic stenosis of 1 vessel (CMI 16%), 96 of 2 or 3 vessels (CMI 81%), 81 celiac artery compression (CMI 25%), and 84 no stenosis (CMI 12%). In total, 138 patients were diagnosed with CMI, rendering a mean incidence of 9.2 (95% confidence interval [CI] 6.2-13.7) per 100,000 inhabitants. Atherosclerotic CMI was most common, with a mean incidence of 7.2 (95% CI 4.6-11.3), followed by median arcuate ligament syndrome 1.3 (95% CI 0.5-3.6) and chronic nonocclusive mesenteric ischemia 0.6 (95% CI 0.2-2.6). The incidence of CMI was highest in female patients (female patients 12.0 [95% CI 7.3-19.6] vs male patients 6.5 [95% CI 3.4-12.5]) and increased with age. CMI was more prevalent in the presence of a ≥70% atherosclerotic single-vessel stenosis of the superior mesenteric artery (40.6%) than the celiac artery (5.6%).
Discussion: The incidence of CMI is higher than previously believed and increases with age. Probability of CMI seems highest in suspected CMI patients with multivessel disease or a ≥70% atherosclerotic single-vessel superior mesenteric artery stenosis.

Gepubliceerd: Clin Transl Gastroenterol. 2020;11(8):e00200.
Impact factor: 3.968; Q2

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22. Fissurectomy combined with botulinum toxin A: a review of short- and long-term efficacy of this treatment strategy for chronic anal fissure; a consecutive proposal of a treatment algorithm for chronic anal fissure
Trzpis M, Klaase JM, Koop RH, Broens PMA.

Background: Several studies have investigated the short- and long-term efficacy of fissurectomy combined with botulinum toxin A injection for patients with chronic anal fissure.
Objective: To evaluate the short- and long-term efficacy of the combined treatment strategy of fissurectomy with botulinum toxin A for chronic anal fissure and to discuss recurrence rates in the light of current theory on the aetiology of anal fissure.
Materials and methods: This is a narrative review. We conducted an article search using PubMed and calculated the means of the reported efficacy ranges.
Results: Fissurectomy combined with botulinum toxin A injections freed at least 78% of the patients from symptoms and yielded a fissure healing rate of up to 86%. Within 12 months after treatment a 3% recurrence rate was reported. On average, the long-term recurrence rate was 22%. One study reported a 50% recurrence rate 22 months after treatment.

Conclusion: The efficacy of fissurectomy combined with botulinum toxin A injection for chronic anal fissure is high. The short-term recurrence rate is low, while long-term recurrence is relatively high. Extended follow-up indicates that recurrence of chronic anal fissure is possibly caused by anal basal pressure building up steadily once again. If so, the cause of renewed increase of pressure should be addressed. Based on the literature and on our clinical experience, we assume that the underlying cause of increasing anal basal pressure is that patients use their pelvic floor muscles inadequately and this in turn leads to chronic anal fissure.

Gepubliceerd: coloproctology. 2020;42:400-8.
Impact factor: nvt; nvt

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23. Textbook Outcome: Nationwide Analysis of a Novel Quality Measure in Pancreatic Surgery
van Roessel S, Mackay TM, van Dieren S, van der Schelling GP, Nieuwenhuijs VB, Bosscha K, van der Harst E, van Dam RM, Liem MSL, Festen S, Stommel MWJ, Roos D, Wit F, Molenaar IQ, de Meijer VE, Kazemier G, de Hingh I, van Santvoort HC, Bonsing BA, Busch OR, Groot Koerkamp B, Besselink MG.

Background: Textbook outcome (TO) is a multidimensional measure for quality assurance, reflecting the "ideal" surgical outcome.
Methods: Post-hoc analysis of patients who underwent pancreatoduodenectomy (PD) or distal pancreatectomy (DP) for all indications between 2014 and 2017, queried from the nationwide prospective Dutch Pancreatic Cancer Audit. An international survey was conducted among 24 experts from 10 countries to reach consensus on the requirements for TO in pancreatic surgery. Univariable and multivariable logistic regression was performed to identify TO predictors. Between-hospital variation in TO rates was compared using observed-versus-expected rates.
Results: Based on the survey (92% response rate), TO was defined by the absence of postoperative pancreatic fistula, bile leak, postpancreatectomy hemorrhage (all ISGPS grade B/C), severe complications (Clavien-Dindo ≥III), readmission, and in-hospital mortality. Overall, 3341 patients were included (2633 (79%) PD and 708 (21%) DP) of whom 60.3% achieved TO; 58.3% for PD and 67.4% for DP. On multivariable analysis, ASA class 3 predicted a worse TO rate after PD (ASA 3 OR 0.59 [0.44-0.80]), whereas a dilated pancreatic duct (>3mm) and pancreatic ductal adenocarcinoma (PDAC) were associated with a better TO rate (OR 2.22 [2.05-3.57] and OR 1.36 [1.14-1.63], respectively). For DP, female sex and the absence of neoadjuvant therapy predicted better TO rates (OR 1.38 [1.01-1.90] and OR 2.53 [1.20-5.31], respectively). When comparing institutions, the observed-versus-expected rate for achieving TO varied from 0.71 to 1.46 per hospital after casemix-adjustment.
Conclusions: TO is a novel quality measure in pancreatic surgery. TO varies considerably between pancreatic centers, demonstrating the potential benefit of quality assurance programs.

Gepubliceerd: Ann Surg. 2020;271(1):155-62.
Impact factor: 10.130; Q1

Totale impact factor: 77.092
Gemiddelde impact factor: 3.352

Aantal artikelen 1e, 2e of laatste auteur: 5
Totale impact factor: 11.216
Gemiddelde impact factor: 2.243

Intensivisten

1. Improving medication safety in the Intensive Care by identifying relevant drug-drug interactions - Results of a multicenter Delphi study
Bakker T, Klopotowska JE, de Keizer NF, van Marum R, van der Sijs H, de Lange DW, de Jonge E, Abu-Hanna A, Dongelmans DA, SIMPLIFY Study Group, includes Beishuizen A, Movig K, Vermeijden JW

Purpose: Drug-drug interactions (DDIs) may cause adverse outcomes in patients admitted to the Intensive Care Unit (ICU). Computerized decision support systems (CDSSs) may help prevent DDIs by timely showing relevant warning alerts, but knowledge on which DDIs are clinically relevant in the ICU setting is limited. Therefore, the purpose of this study was to identify DDIs relevant for the ICU.
Materials And Methods: We conducted a modified Delphi procedure with a Dutch multidisciplinary expert panel consisting of intensivists and hospital pharmacists to assess the clinical relevance of DDIs for the ICU. The procedure consisted of two rounds, each included a questionnaire followed by a live consensus meeting.
Results: In total the clinical relevance of 148 DDIs was assessed, of which agreement regarding the relevance was reached for 139 DDIs (94%). Of these 139 DDIs, 53 (38%) were considered not clinically relevant for the ICU setting.
Conclusions: A list of clinically relevant DDIs for the ICU setting was established on a national level. The clinical value of CDSSs for medication safety could be improved by focusing on the identified clinically relevant DDIs, thereby avoiding alert fatigue.

Gepubliceerd: J Crit Care. 2020;57:134-40.
Impact factor: 2.685; Q3

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2. Prevalence and management of delirium in intensive care units in the Netherlands: An observational multicentre study
Berger E, Wils EJ, Vos P, van Santen S, Koets J, Slooter AJC, van der Woude M, Koopmans M, Rinket MA, Hoiting O, Hoogendoorn EE, Streefkerk JO, de Vreede EW, Riekerk B, Simons KS, Toscano E, Schoonderbeek FJ, Hofstra LS, van den Oever HLA, Raben A, Holman S, Nooteboom F, Bethlehem C, Ten Cate J, Verkade M, Mijzen L, de Man-van Ginkel JM, Vermeulen H, van den Boogaard MR.

Objectives: This study aimed to determine the prevalence, risk factors of delirium and current practice of delirium management in intensive care units of various levels of care.
Research Methodology/Design: Prospective multicentre cohort study.
Setting: In all adult patients admitted to one of the participating intensive care units on World Delirium Awareness Day 2018, delirium point and period prevalence rates were measured between ICU admission and seven days after the index day.
Results: In total, 28 (33%) Dutch intensive care units participated in this study. Point-prevalence was 23% (range 41), and period-prevalence was 42% (range 70). University intensive care units had a significantly higher delirium point-prevalence compared with non-university units (26% vs.15%, p = 0.02). No significant difference were found in period prevalence (50% vs. 39%, p = 0.09). Precipitating risk factors, infection and mechanical ventilation differed significantly between delirium and non-

delirium patients. No differences were observed for predisposing risk factors. A delirium protocol was present in 89% of the ICUs. Mean delirium assessment compliance measured was 84% (±19) in 14 units and estimated 59% (±29) in the other 14.
Conclusion: Delirium prevalence in Dutch intensive care units is substantial and occurs with a large variation, with the highest prevalence in university units. Precipitating risk factors were more frequent in patients with delirium. In the majority of units a delirium management protocol is in place.

Gepubliceerd: Intensive Crit Care Nurs. 2020;61:102925.
Impact factor: 1.886; Q1

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3. Attitudes of Dutch intensive care unit clinicians towards oxygen therapy
Grim CCA, Cornet AD, Kroner A, Meiners AJ, Brouwers A, Reidinga AC, van Westerloo DJ, Bergmans D, Gommers D, Versluis D, Weller D, Christiaan Boerma E, van Driel E, de Jonge E, Schoonderbeek FJ, Helmerhorst HJF, Jongsma-van Netten HG, Weenink J, Woittiez KJ, Simons KS, van Ewelie L, Petjak M, Sigtermans MJ, van der Woude M, Cremer OL, Bijlstra P, van der Heiden P, So RKL, Vink R, Jansen T, de Ruijter W.

Background: Over the last decade, there has been an increasing awareness for the potential harm of the administration of too much oxygen. We aimed to describe self-reported attitudes towards oxygen therapy by clinicians from a large representative sample of intensive care units (ICUs) in the Netherlands.
Methods: In April 2019, 36 ICUs in the Netherlands were approached and asked to send out a questionnaire (59 questions) to their nursing and medical staff (ICU clinicians) eliciting self-reported behaviour and attitudes towards oxygen therapy in general and in specific ICU case scenarios.
Results: In total, 1361 ICU clinicians (71% nurses, 24% physicians) from 28 ICUs returned the questionnaire. Of responding ICU clinicians, 64% considered oxygen-induced lung injury to be a major concern. The majority of respondents considered a partial pressure of oxygen (PaO2) of 6-10 kPa (45-75 mmHg) and an arterial saturation (SaO2) of 85-90% as acceptable for 15 minutes, and a PaO2 7-10 kPa (53-75 mmHg) and SaO2 90-95% as acceptable for 24-48 hours in an acute respiratory distress syndrome (ARDS) patient. In most case scenarios, respondents reported not to change the fraction of inspired oxygen (FiO2) if SaO2 was 90-95% or PaO2 was 12 kPa (90 mmHg).
Conclusion: A representative sample of ICU clinicians from the Netherlands were concerned about oxygen-induced lung injury, and reported that they preferred PaO2 and SaO2 targets in the lower physiological range and would adjust ventilation settings accordingly.

Gepubliceerd: Neth J Med. 2020;78(4):167-74.
Impact factor: 0.967; Q4

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4. Association of kidney function with effectiveness of procalcitonin-guided antibiotic treatment: a patient-level meta-analysis from randomized controlled trials

Heilmann E, Gregoriano C, Wirz Y, Luyt CE, Wolff M, Chastre J, Tubach F, Christ-Crain M, Bouadma L, Annane D, Damas P, Kristoffersen KB, Oliveira CF, Stolz D, Tamm M, de Jong E, Reinhart K, Shehabi Y, Verduri A, Nobre V, Nijsten M, deLange DW, van Oers JAH, Beishuizen A, Girbes ARJ, Mueller B, Schuetz P.

Objectives: Patients with impaired kidney function have a significantly slower decrease of procalcitonin (PCT) levels during infection. Our aim was to study PCT-guided antibiotic stewardship and clinical outcomes in patients with impairments of kidney function as assessed by creatinine levels measured upon hospital admission.
Methods: We pooled and analyzed individual data from 15 randomized controlled trials who were randomly assigned to receive antibiotic therapy based on a PCT-algorithms or based on standard of care. We stratified patients on the initial glomerular filtration rate (GFR, ml/min/1.73 m2) in three groups (GFR >90 [chronic kidney disease; CKD 1], GFR 15-89 [CKD 2-4] and GFR<15 [CKD 5]). The main efficacy and safety endpoints were duration of antibiotic treatment and 30-day mortality.
Results: Mean duration of antibiotic treatment was significantly shorter in PCT-guided (n=2,492) compared to control patients (n=2,510) (9.5-7.6 days; adjusted difference in days -2.01 [95% CI, -2.45 to -1.58]). CKD 5 patients had overall longer treatment durations, but a 2.5-day reduction in treatment duration was still found in patients receiving in PCT-guided care (11.3 vs. 8.6 days [95% CI -3.59 to -1.40]). There were 397 deaths in 2,492 PCT-group patients (15.9%) compared to 460 deaths in 2,510 control patients (18.3%) (adjusted odds ratio, 0.88 [95% CI 0.78 to 0.98)]. Effects of PCT-guidance on antibiotic treatment duration and mortality were similar in subgroups stratified by infection type and clinical setting (p interaction >0.05).
Conclusions: This individual patient data meta-analysis confirms that the use of PCT in patients with impaired kidney function, as assessed by admission creatinine levels, is associated with shorter antibiotic courses and lower mortality rates.

Gepubliceerd: Clin Chem Lab Med. 2020;59(2):441-53.
Impact factor: 3.595; Q1

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5. Early high protein intake and mortality in critically ill ICU patients with low skeletal muscle area and -density
Looijaard W, Dekker IM, Beishuizen A, Girbes ARJ, Oudemans-van Straaten HM, Weijs PJM.

Background and Aims: Optimal nutritional support during the acute phase of critical illness remains controversial. We hypothesized that patients with low skeletal muscle area and -density may specifically benefit from early high protein intake. Aim of the present study was to determine the association between early protein intake (day 2-4) and mortality in critically ill intensive care unit (ICU) patients with normal skeletal muscle area, low skeletal muscle area, or combined low skeletal muscle area and -density.
Methods: Retrospective database study in mechanically ventilated, adult critically ill patients with an abdominal CT-scan suitable for skeletal muscle assessment around ICU admission, admitted from January 2004 to January 2016 (n = 739). Patients received protocolized nutrition with protein target 1.2-1.5 g/kg/day. Skeletal muscle

area and -density were assessed on abdominal CT-scans at the 3rd lumbar vertebra level using previously defined cut-offs.
Results: Of 739 included patients (mean age 58 years, 483 male (65%), APACHE II score 23), 294 (40%) were admitted with normal skeletal muscle area and 445 (60%) with low skeletal muscle area. Two hundred (45% of the low skeletal muscle area group) had combined low skeletal muscle area and -density. In the normal skeletal muscle area group, no significant associations were found. In the low skeletal muscle area group, higher early protein intake was associated with lower 60-day mortality (adjusted hazard ratio (HR) per 0.1 g/kg/day 0.82, 95%CI 0.73-0.94) and lower 6-month mortality (HR 0.88, 95%CI 0.79-0.98). Similar associations were found in the combined low skeletal muscle area and -density subgroup (HR 0.76, 95%CI 0.64-0.90 for 60-day mortality and HR 0.80, 95%CI 0.68-0.93 for 6-month mortality).
Conclusions: Early high protein intake is associated with lower mortality in critically ill patients with low skeletal muscle area and -density, but not in patients with normal skeletal muscle area on admission. These findings may be a further step to personalized nutrition, although randomized studies are needed to assess causality.

Gepubliceerd: Clin Nutr. 2020;39(7):2192-201.
Impact factor: 6.360; Q1

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6. Caspofungin Weight-Based Dosing Supported by a Population Pharmacokinetic Model in Critically Ill Patients
Märtson AG, van der Elst KCM, Veringa A, Zijlstra JG, Beishuizen A, van der Werf TS, Kosterink JGW, Neely M, Alffenaar JW.

The objective of this study was to develop a population pharmacokinetic model and to determine a dosing regimen for caspofungin in critically ill patients. Nine blood samples were drawn per dosing occasion. Fifteen patients with (suspected) invasive candidiasis had one dosing occasion and five had two dosing occasions, measured on day 3 (±1) of treatment. Pmetrics was used for population pharmacokinetic modeling and probability of target attainment (PTA). A target 24-h area under the concentration-time curve (AUC) value of 98 mg·h/liter was used as an efficacy parameter. Secondarily, the AUC/MIC targets of 450, 865, and 1,185 were used to calculate PTAs for Candida glabrata, C. albicans, and C. parapsilosis, respectively. The final 2-compartment model included weight as a covariate on volume of distribution (V). The mean V of the central compartment was 7.71 (standard deviation [SD], 2.70) liters/kg of body weight, the mean elimination constant (K(e)) was 0.09 (SD, 0.04) h(-1), the rate constant for the caspofungin distribution from the central to the peripheral compartment was 0.44 (SD, 0.39) h(-1), and the rate constant for the caspofungin distribution from the peripheral to the central compartment was 0.46 (SD, 0.35) h(-1) A loading dose of 2 mg/kg on the first day, followed by 1.25 mg/kg as a maintenance dose, was chosen. With this dose, 98% of the patients were expected to reach the AUC target on the first day and 100% of the patients on the third day. The registered caspofungin dose might not be suitable for critically ill patients who were all overweight (≥120 kg), over 80% of median weight (78 kg), and around 25% of lower weight (≤50 kg). A weight-based dose regimen might be appropriate for achieving adequate exposure of caspofungin in intensive care unit patients.

Gepubliceerd: Antimicrob Agents Chemother. 2020;64(9):e00905-20.

Impact factor: 4.904; Q1

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7. A cross-sectional investigation of communication in Do-Not-Resuscitate orders in Dutch hospitals
Schluep M, Hoeks SE, Endeman H, S IJ, Romijn TMM, Alsma J, Bosch FH, Cornet AD, Knook AHM, Koopman-van Gemert A, van Melsen T, Peters R, Simons KS, Wils EJ, Stolker RJ, van Dijk M.

Background: The decision to attempt or refrain from resuscitation is preferably based on prognostic factors for outcome and subsequently communicated with patients. Both patients and physicians consider good communication important, however little is known about patient involvement in and understanding of cardiopulmonary resuscitation (CPR) directives. AIM: To determine the prevalence of Do Not Resuscitate (DNR)-orders, to describe recollection of CPR-directive conversations and factors associated with patient recollection and understanding.
Methods: This was a two-week nationwide multicentre cross-sectional observational study using a study-specific survey. The study population consisted of patients admitted to non-monitored wards in 13 hospitals. Data were collected from the electronic medical record (EMR) concerning CPR-directive, comorbidity and at-home medication. Patients reported their perception and expectations about CPR-counselling through a questionnaire.
Results: A total of 1136 patients completed the questionnaire. Patients' CPR-directives were documented in the EMR as follows: 63.7% full code, 27.5% DNR and in 8.8% no directive was documented. DNR was most often documented for patients >80 years (66.4%) and in patients using >10 medications (45.3%). Overall, 55.8% of patients recalled having had a conversation about their CPR-directive and 48.1% patients reported the same CPR-directive as the EMR. Most patients had a good experience with the CPR-directive conversation in general (66.1%), as well as its timing (84%) and location (94%) specifically.
Conclusions: The average DNR-prevalence is 27.5%. Correct understanding of their CPR-directive is lowest in patients aged ≥80 years and multimorbid patients. CPR-directive counselling should focus more on patient involvement and their correct understanding.

Gepubliceerd: Resuscitation. 2020;154:52-60.
Impact factor: 4.215; Q1

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8. Data on sex differences in one-year outcomes of out-of-hospital cardiac arrest patients without ST-segment elevation
Spoormans EM, Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, van de Ven PM, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak R, Vlachojannis GJ, Eikemans BJW, van der Harst P, van der Horst ICC, Voskuil M, van der Heijden JJ, Beishuizen A, Stoel M, Camaro C, van der Hoeven H, Henriques JP, Vlaar APJ, Vink MA, van den Bogaard B, Heestermans T, de Ruijter W, Delnoij TSR, Crijns H, Jessurun GAJ, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, Appelman Y, van Royen N.

Sex differences in out-of-hospital cardiac arrest (OHCA) patients are increasingly recognized. Although it has been found that post-resuscitated women are less likely to have significant coronary artery disease (CAD) than men, data on follow-up in these patients are limited. Data for this data in brief article was obtained as a part of the randomized controlled Coronary Angiography after Cardiac Arrest without ST-segment elevation (COACT) trial. The data supplements the manuscript "Sex differences in out-of-hospital cardiac arrest patients without ST-segment elevation: A COACT trial substudy" were it was found that women were less likely to have significant CAD including chronic total occlusions, and had worse survival when CAD was present. The dataset presented in this paper describes sex differences on interventions, implantable-cardioverter defibrillator (ICD) shocks and hospitalizations due to heart failure during one-year follow-up in patients successfully resuscitated after OHCA. Data was derived through a telephone interview at one year with the patient or general practitioner. Patients in this randomized dataset reflects a homogenous study population, which can be valuable to further build on research regarding long-term sex differences and to further improve cardiac care.

Gepubliceerd: Data Brief. 2020;33:106521.
Impact factor: nvt; nvt

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9. Influence of sedation on delirium recognition in critically ill patients: A multinational cohort study

van den Boogaard M, Wassenaar A, van Haren FMP, Slooter AJC, Jorens PG, van der Jagt M, Simons KS, Egerod I, Burry LD, Beishuizen A, Pickkers P, Devlin JW.

Background: Guidelines advocate intensive care unit (ICU) patients be regularly assessed for delirium using either the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC). Single-centre studies, primarily with the CAM-ICU, suggest level of sedation may influence delirium screening results.
Objective: The objective of this study was to determine the association between level of sedation and delirium occurrence in critically ill patients assessed with either the CAM-ICU or the ICDSC.
Methods: This was a secondary analysis of a multinational, prospective cohort study performed in nine ICUs from seven countries. Consecutive ICU patients with a Richmond Agitation-Sedation Scale (RASS) of -3 to 0 at the time of delirium assessment where a RASS ≤ 0 was secondary to a sedating medication. Patients were assessed with either the CAM-ICU or the ICDSC. Logistic regression analysis was used to account for factors with the potential to influence level of sedation or delirium occurrence.
Results: Among 1660 patients, 1203 patients underwent 5741 CAM-ICU assessments [9.6% were delirium positive; at RASS = 0 (3.3% were delirium positive), RASS = -1 (19.3%), RASS = -2 (35.1%); RASS = -3 (39.0%)]. The other 457 patients underwent 3210 ICDSC assessments [11.6% delirium positive; at RASS = 0 (4.9% were delirium positive), RASS = -1 (15.8%), RASS = -2 (26.6%); RASS = -3 (20.6%)]. A RASS of -3 was associated with more positive delirium evaluations (odds ratio: 2.31; 95% confidence interval: 1.34-3.98) in the CAM-ICU-assessed patients (vs. the ICDSC-assessed patients). At a RASS of 0, assessment with the CAM-ICU (vs. the ICDSC) was associated with fewer positive delirium

evaluations (odds ratio: 0.58; 95% confidence interval: 0.43-0.78). At a RASS of -1 or -2, no association was found between the delirium assessment method used (i.e., CAM-ICU or ICDSC) and a positive delirium evaluation.
Conclusions: The influence of level of sedation on a delirium assessment result depends on whether the CAM-ICU or ICDSC is used. Bedside ICU nurses should consider these results when evaluating their sedated patients for delirium. Future research is necessary to compare the CAM-ICU and the ICDSC simultaneously in sedated and nonsedated ICU patients.
Trial registration: ClinicalTrials.gov; NCT02518646.

Gepubliceerd: Aust Crit Care. 2020;33(5):420-5.
Impact factor: 2.214; Q1

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10. Rare metastatic seeding: endogenous endophtalmitis in Staphylococcus aureus sepsis
van der Weert S, Lansink PJ, Vermeijden JW, Cornet AD.

Gepubliceerd: Intensive Care Med. 2020;46(3):536-7.
Impact factor: 17.679; Q1

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11. Coronary Angiography After Cardiac Arrest Without ST Segment Elevation: One-Year Outcomes of the COACT Randomized Clinical Trial
Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen MM, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak RR, Vlachojannis GJ, Eikemans BJW, van der Harst P, van der Horst ICC, Voskuil M, van der Heijden JJ, Beishuizen A, Stoel M, Camaro C, van der Hoeven H, Henriques JP, Vlaar APJ, Vink MA, van den Bogaard B, Heestermans T, de Ruijter W, Delnoij TSR, Crijns H, Jessurun GAJ, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, Spoormans EM, van de Ven PM, Oudemans-van Straaten HM, van Royen N.

Importance: Ischemic heart disease is a common cause of cardiac arrest. However, randomized data on long-term clinical outcomes of immediate coronary angiography and percutaneous coronary intervention (PCI) in patients successfully resuscitated from cardiac arrest in the absence of ST segment elevation myocardial infarction (STEMI) are lacking.
Objective: To determine whether immediate coronary angiography improves clinical outcomes at 1 year in patients after cardiac arrest without signs of STEMI, compared with a delayed coronary angiography strategy.
Design, Setting, and Participants: A prespecified analysis of a multicenter, open-label, randomized clinical trial evaluated 552 patients who were enrolled in 19 Dutch centers between January 8, 2015, and July 17, 2018. The study included patients who experienced out-of-hospital cardiac arrest with a shockable rhythm who were successfully resuscitated without signs of STEMI. Follow-up was performed at 1 year. Data were analyzed, using the intention-to-treat principle, between August 29 and October 10, 2019.
Interventions: Immediate coronary angiography and PCI if indicated or coronary angiography and PCI if indicated, delayed until after neurologic recovery.

Main Outcomes and Measures: Survival, myocardial infarction, revascularization, implantable cardiac defibrillator shock, quality of life, hospitalization for heart failure, and the composite of death or myocardial infarction or revascularization after 1 year.
Results: At 1 year, data on 522 of 552 patients (94.6%) were available for analysis. Of these patients, 413 were men (79.1%); mean (SD) age was 65.4 (12.3) years. A total of 162 of 264 patients (61.4%) in the immediate angiography group and 165 of 258 patients (64.0%) in the delayed angiography group were alive (odds ratio, 0.90; 95% CI, 0.63-1.28). The composite end point of death, myocardial infarction, or repeated revascularization since the index hospitalization was met in 112 patients (42.9%) in the immediate group and 104 patients (40.6%) in the delayed group (odds ratio, 1.10; 95% CI, 0.77-1.56). No significant differences between the groups were observed for the other outcomes at 1-year follow-up. For example, the rate of ICD shocks was 20.4% in the immediate group and 16.2% in the delayed group (odds ratio, 1.32; 95% CI, 0.66-2.64).
Conclusions and Relevance: In this trial of patients successfully resuscitated after out-of-hospital cardiac arrest and without signs of STEMI, a strategy of immediate angiography was not found to be superior to a strategy of delayed angiography with respect to clinical outcomes at 1 year. Coronary angiography in this patient group can therefore be delayed until after neurologic recovery without affecting outcomes.
Trial registration: trialregister.nl Identifier: NTR4973.

Gepubliceerd: JAMA Cardiol. 2020;5(12):1-8.
Impact factor: 12.794; Q1

Totale impact factor: 57.299
Gemiddelde impact factor: 5.209

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 18.646
Gemiddelde impact factor: 9.323

Interne Geneeskunde

1. Surgery for Unresectable Stage IIIC and IV Melanoma in the Era of New Systemic Therapy
Blankenstein SA, Aarts MJB, van den Berkmortel F, Boers-Sonderen MJ, van den Eertwegh AJM, Franken MG, de Groot JWB, Haanen J, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, Wouters M, van Akkooi ACJ.

Opportunities for surgical treatment in metastatic melanoma patients have re-emerged due to the development of novel systemic therapeutics over the past decade. The aim of this study is to present data on outcomes of surgery in patients with unresectable stage IIIC and IV melanoma, who have previously been treated with immunotherapy or targeted therapy. Data was extracted from the Dutch Melanoma Treatment Registry (DMTR) on 154 patients obtaining disease control to systemic therapy and undergoing subsequent surgery. Disease control was defined as a complete response (CR), which was seen in 3.2% of patients; a partial response (PR), seen in 46.1% of patients; or stable disease (SD), seen in 44.2% of patients. At a median follow-up of 10.0 months (interquartile range 4-22) after surgery, the median overall survival (OS) had not been reached in our cohort and median progression-free survival (PFS) was 9.0 months (95% CI 6.3-11.7). A CR or PR at first follow-up after surgery was associated with both a better OS and PFS compared to stable or progressive disease ($p < 0.001$). We conclude that selected patients can benefit from surgery after achieving disease control with systemic therapy.

Gepubliceerd: Cancers (Basel). 2020;12(5).
Impact factor: 6.126; Q1

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2. The GALANT trial: study protocol of a randomised placebo-controlled trial in patients with a (68) Ga -DOTATATE PET-positive, clinically non-functioning pituitary macroadenoma on the effect of lan reotide on tumour size
Boertien TM, Drent ML, Booij J, Majoie C, Stokkel MPM, Hoogmoed J, Pereira A, Biermasz NR, Simsek S, Groote Veldman R, Tanck MWT, Fliers E, Bisschop PH.

Introduction: At present, there is no approved medical treatment option for patients with non-functioning pituitary adenoma. A number of open-label studies suggest that treatment with somatostatin analogues may prevent tumour progression. In vivo somatostatin receptor imaging using (68)Ga-DOTATATE PET (PET, positron emission tomography) could help in preselecting patients potentially responsive to treatment. Our aim is to investigate the effect of the somatostatin analogue lanreotide as compared with placebo on tumour size in patients with a (68)Ga-DOTATATE PET-positive non-functioning pituitary macroadenoma (NFMA).
Methods and Analysis: The GALANT study is a multicentre, randomised, double-blind, placebo-controlled trial in adult patients with a suprasellar extending NFMA. Included patients undergo a (68)Ga-DOTATATE PET/CT of the head and tracer uptake is assessed after coregistration with pituitary MRI. Forty-four patients with a (68)Ga-DOTATATE PET-positive NFMA are randomised in a 1:1 ratio between lanreotide 120 mg or placebo, both administered as subcutaneous injections every 28

days for 72 weeks. The primary outcome is the change in cranio-caudal tumour diameter on pituitary MRI after treatment. Secondary outcomes are change in tumour volume, time to tumour progression, change in quality of life and number of adverse events. Final results are expected in the second half of 2021.
Ethics and Dissemination: The study protocol has been approved by the Medical Research Ethics Committee of the Academic Medical Centre (AMC) of the Amsterdam University Medical Centres and by the Dutch competent authority. It is an investigator-initiated study with financial support by Ipsen Farmaceutica BV. The AMC, as sponsor, remains owner of all data. Results will be submitted for publication in a peer-reviewed journal.
Trial registration number: NL5136 (Netherlands Trial Register); pre-recruitment.

Gepubliceerd: BMJ Open. 2020;10(8):e038250.
Impact factor: 2.496; Q2

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3. Response and Adherence to Nilotinib in Daily practice (RAND study): an in-depth observational study of chronic myeloid leukemia patients treated with nilotinib
Boons C, Timmers L, Janssen J, Westerweel PE, Blijlevens NMA, Smit WM, Bartelink IH, Wilschut JA, Swart EL, Hendrikse NH, Hugtenburg JG.

Introduction: This comprehensive observational study aimed to gain insight into adherence to nilotinib and the effect of (non)adherence on exposure (Cmin) and treatment outcomes.
Methods: Chronic myeloid leukemia (CML) patients using nilotinib were followed for 12 months. Adherence was measured by Medication Event Monitoring System (MEMS), pill count, and Medication Adherence Report Scale (MARS-5). Nilotinib Cmin and patient-reported outcomes (i.e., quality of life, side effects, beliefs, satisfaction) were measured at baseline, 3, 6, and 12 months.
Results: Sixty-eight patients (57.5 +/- 15.0 years, 49% female) participated. Median adherence to nilotinib (MEMS and pill count) was >/= 99% and adherence < 90% was rare. Self-reported nonadherence (MARS-5) increased in the first year of treatment to a third of patients. In line with the strong beliefs in the necessity of taking nilotinib, forgetting to take a dose was more prevalent than intentionally adjusting/skipping doses. Nilotinib Cmin were generally above the therapeutic target in 95% of patients. Patients reported a variety of side effects, of which fatigue was most frequent. The mean Cmin was higher in patients who reported severe itching and fatigue. The overall 1-year MMR rate ranged from 47 to 71%.
Conclusion: Substantial nonadherence (< 90%) to nilotinib was rare and nilotinib Cmin were generally above the therapeutic target. Lack of response in our group of patients was not related to nonadherence or inadequate Cmin. Nevertheless, a considerable number of patients experienced difficulties in adhering to the twice daily fasted dosing regimen, emphasizing the importance of continuous support of medication adherence in CML. CLINICAL
Trial registration: NTR3992 (Netherlands Trial Register, www.trialregister.nl).

Gepubliceerd: Eur J Clin Pharmacol. 2020;76(9):1213-26.
Impact factor: 2.641; Q3

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4. Prediction admission in the older population in the Emergency Department: the CLEARED tool
Brink A, Alsma J, Brink HS, de Gelder J, Lucke JA, Mooijaart SP, Zietse R, Schuit SCE, Lingsma HF.

Background: Length of stay (LOS) in the Emergency Department (ED) is correlated with an extended in-hospital LOS and may even increase 30-day mortality. Older patients represent a growing population in the ED and they are especially at risk of adverse outcomes. Screening tools that adequately predict admission could help reduce waiting times in the ED and reduce time to treatment. We aimed to develop and validate a clinical prediction tool for admission, applicable to the aged patient population in the ED.
Methods: Data from 7,606 ED visits of patients aged 70 years and older between 2012 and 2014 were used to develop the CLEARED tool. Model performance was assessed with discrimination using logistic regression and calibration. The model was internally validated by bootstrap resampling in Erasmus Medical Center and externally validated at two other hospitals, Medisch Spectrum Twente (MST) and Leiden University Medical Centre (LUMC).
Results: CLEARED contains 10 predictors: body temperature, heart rate, diastolic blood pressure, systolic blood pressure, oxygen saturation, respiratory rate, referral status, the Manchester Triage System category, and the need for laboratory or radiology testing. The internally validated area under the curve (AUC) was 0.766 (95% CI [0.759;0.781]). External validation in MST showed an AUC of 0.797 and in LUMC, an AUC of 0.725.
Conclusions: The developed CLEARED tool reliably predicts admission in elderly patients visiting the ED. It is a promising prompt, although further research is needed to implement the tool and to investigate the benefits in terms of reduction of crowding and LOS in the ED.

Gepubliceerd: Neth J Med. 2020;78(6):357-67.
Impact factor: 0.967; Q4

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5. Efficacy of α-Blockers on Hemodynamic Control during Pheochromocytoma Resection: A Randomized Controlled Trial
Buitenwerf E, Osinga TE, Timmers H, Lenders JWM, Feelders RA, Eekhoff EMW, Haak HR, Corssmit EPM, Bisschop P, Valk GD, Groote Veldman R, Dullaart RPF, Links TP, Voogd MF, Wietasch G, Kerstens MN.

Context: Pretreatment with α-adrenergic receptor blockers is recommended to prevent hemodynamic instability during resection of a pheochromocytoma or sympathetic paraganglioma (PPGL).
Objective: To determine which type of α-adrenergic receptor blocker provides the best efficacy.
Design: Randomized controlled open-label trial (PRESCRIPT; ClinicalTrials.gov NCT01379898).
Setting: Multicenter study including 9 centers in The Netherlands.
Patients: 134 patients with nonmetastatic PPGL.

Intervention: Phenoxybenzamine or doxazosin starting 2 to 3 weeks before surgery using a blood pressure targeted titration schedule. Intraoperative hemodynamic management was standardized.
Main Outcome Measures: Primary efficacy endpoint was the cumulative intraoperative time outside the blood pressure target range (ie, SBP >160 mmHg or MAP <60 mmHg) expressed as a percentage of total surgical procedure time. Secondary efficacy endpoint was the value on a hemodynamic instability score.
Results: Median cumulative time outside blood pressure targets was 11.1% (interquartile range [IQR]: 4.3-20.6] in the phenoxybenzamine group compared to 12.2% (5.3-20.2)] in the doxazosin group (P = .75, r = 0.03). The hemodynamic instability score was 38.0 (28.8-58.0) and 50.0 (35.3-63.8) in the phenoxybenzamine and doxazosin group, respectively (P = .02, r = 0.20). The 30-day cardiovascular complication rate was 8.8% and 6.9% in the phenoxybenzamine and doxazosin group, respectively (P = .68). There was no mortality after 30 days.
Conclusions: The duration of blood pressure outside the target range during resection of a PPGL was not different after preoperative treatment with either phenoxybenzamine or doxazosin. Phenoxybenzamine was more effective in preventing intraoperative hemodynamic instability, but it could not be established whether this was associated with a better clinical outcome.

Gepubliceerd: J Clin Endocrinol Metab. 2020;105(7):2381-91.
Impact factor: 5.399; Q1

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6. Treatment of patients with MYC rearrangement positive large B-cell lymphoma with R-CHOP plus lenalidomide: results of a multicenter HOVON phase II trial
Chamuleau MED, Burggraaff CN, Nijland M, Bakunina K, Mous R, Lugtenburg PJ, Dierickx D, van Imhoff GW, Vermaat JSP, Marijt EAF, Visser O, Mandigers C, Bilgin YM, Beeker A, Durian MF, van Rees B, Bohmer LH, Tick LW, Boersma RS, Snijders TJF, Schouten HC, Koene HR, de Jongh E, Hijmering N, Diepstra A, van den Berg A, Arens AIJ, Huijbregts J, Hoekstra O, Zijlstra JM, de Jong D, Kersten MJ.

Patients with MYC-rearrangement positive large B-cell lymphoma (MYC+ LBCL) have an inferior prognosis following standard first-line therapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) as compared to patients without MYC rearrangement. Although intensive chemotherapy regimens yield higher remission rates, toxicity remains a concern. Lenalidomide is an oral immunomodulatory drug which downregulates MYC and its target genes thereby providing support using lenalidomide as additional therapeutic option for MYC+ LBCL. A phase II trial was conducted evaluating the efficacy of lenalidomide (15 mg day 1-14) in combination with R-CHOP (R2CHOP) in newly diagnosed MYC+ LBCL patients identified through a nationwide MYC-FISH screening program. The primary endpoint was complete metabolic response (CMR) on centrally reviewed 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)-computer tomography (CT)-scan at end-of-treatment. Secondary endpoints were overall survival (OS), disease-free survival (DFS) and event-free survival (EFS). Eighty-two patients with stage II-IV MYC+ LBCL were treated with 6 cycles of R2CHOP. At EOT, 67% (confidence interval (CI) 58-75%) of the patients reached CMR. With a median follow-up of 25.4 months, 2-year estimates (95% CI) for OS, DFS, EFS were 73%

(62-82%), 75% (63-84%) and 63% (52-73%) respectively. In this prospective trial for newly diagnosed MYC+ LBCL patients, we found that administering R2CHOP was safe, and yields comparable CMR and survival rates as in studies applying more intensive chemotherapy regimens. Hence, these findings offer new prospects for MYC+ LBCL patients and warrant comparison in prospective randomized clinical trials. This trial was registered at www.clinicaltrialsregister.eu (#2014-002654-39).

Gepubliceerd: Haematologica. 2020;105(12):2805-12.
Impact factor: 7.116; Q1

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7. Bortezomib maintenance after R-CHOP, cytarabine and autologous stem cell transplantation in newly diagnosed patients with mantle cell lymphoma, results of a randomised phase II HOVON trial
Doorduijn JK, Zijlstra JM, Lugtenburg PJ, Kersten MJ, Bohmer LH, Minnema MC, MacKenzie MA, van Marwijk Kooij R, de Jongh E, Snijders TJF, de Weerdt O, van Gelder M, Hoogendoorn M, Leys RBL, Kibbelaar RE, de Jong D, Chitu DA, Van't Veer MB, Kluin-Nelemans HC.

Rituximab-containing induction followed by autologous stem cell transplantation (ASCT) is the standard first-line treatment for young mantle cell lymphoma patients. However, most patients relapse after ASCT. We investigated in a randomised phase II study the outcome of a chemo-immuno regimen and ASCT with or without maintenance therapy with bortezomib. Induction consisted of three cycles R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), two cycles high-dose cytarabine, BEAM (carmustine, etoposide, cytarabine, melphalan) and ASCT. Patients responding were randomised between bortezomib maintenance (1.3 mg/m(2) intravenously once every 2 weeks, for 2 years) and observation. Of 135 eligible patients, 115 (85%) proceeded to ASCT, 60 (44%) were randomised. With a median follow-up of 77.5 months for patients still alive, 5-year event-free survival (EFS) was 51% (95% CI 42-59%); 5-year overall survival (OS) was 73% (95% CI 65-80%). The median follow-up of randomised patients still alive was 71.5 months. Patients with bortezomib maintenance had a 5-year EFS of 63% (95% CI 44-78%) and 5-year OS of 90% (95% CI 72-97%). The patients randomised to observation had 5-year PFS of 60% (95% CI, 40-75%) and OS of 90% (95% CI 72-97%). In conclusion, in this phase II study we found no indication of a positive effect of bortezomib maintenance after ASCT.

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Impact factor: 5.518; Q1

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8. Ibrutinib added to 10-day decitabine for older patients with AML and higher risk MDS
Huls G, Chitu DA, Pabst T, Klein SK, Stussi G, Griskevicius L, Valk PJM, Cloos J, van de Loosdrecht AA, Breems D, van Lammeren-Venema D, van Zeventer I, Boersma R, Jongen-Lavrencic M, Fehr M, Hoogendoorn M, Manz MG, Sohne M, van Marwijk Kooy R, Deeren D, van der Poel MWM, Legdeur MC, Tick L, Chalandon Y, Ammatuna E, Blum S, Lowenberg B, Ossenkoppele GJ.

The treatment of older, unfit patients with acute myeloid leukemia (AML) is challenging. Based on preclinical data of Bruton tyrosine kinase expression/phosphorylation and ibrutinib cytotoxicity in AML blasts, we conducted a randomized phase 2 multicenter study to assess the tolerability and efficacy of the addition of ibrutinib to 10-day decitabine in unfit (ie, Hematopoietic Cell Transplantation Comorbidity Index >/=3) AML patients and higher risk myelodysplasia patients (HOVON135/SAKK30/15 trial). In total, 144 eligible patients were randomly (1:1) assigned to either 10-day decitabine combined with ibrutinib (560 mg; sequentially given, starting the day after the last dose of decitabine) (n = 72) or to 10-day decitabine (n = 72). The addition of ibrutinib was well tolerated, and the number of adverse events was comparable for both arms. In the decitabine plus ibrutinib arm, 41% reached complete remission/complete remission with incomplete hematologic recovery (CR/CRi), the median overall survival (OS) was 11 months, and 2-year OS was 27%; these findings compared with 50% CR/CRi, median OS of 11.5 months, and 2-year OS of 21% for the decitabine group (not significant). Extensive molecular profiling at diagnosis revealed that patients with STAG2, IDH2, and ASXL1 mutations had significantly lower CR/CRi rates, whereas patients with mutations in TP53 had significantly higher CR/CRi rates. Furthermore, multicolor flow cytometry revealed that after 3 cycles of treatment, 28 (49%) of 57 patients with available bone marrow samples had no measurable residual disease. In this limited number of cases, measurable residual disease revealed no apparent impact on event-free survival and OS. In conclusion, the addition of ibrutinib does not improve the therapeutic efficacy of decitabine. This trial was registered at the Netherlands Trial Register (NL5751 [NTR6017]) and has EudraCT number 2015-002855-85.

Gepubliceerd: Blood Adv. 2020;4(18):4267-77.
Impact factor: 4.910; Q1

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9. Myocardial dysfunction in long-term breast cancer survivors treated at ages 40-50 years

Jacobse JN, Steggink LC, Sonke GS, Schaapveld M, Hummel YM, Steenbruggen TG, Lefrandt JD, Nuver J, Crijns APG, Aleman BMP, van der Meer P, Gietema JA, van Leeuwen FE.

Aims: Anthracyclines increase heart failure (HF) risk, but the long-term prevalence of myocardial dysfunction in young breast cancer (BC) survivors is unknown. Early measures of left ventricular myocardial dysfunction are needed to identify BC patients at risk of symptomatic HF.
Methods and Results: Within an established cohort, we studied markers for myocardial dysfunction among 569 women, who were 5-7 years (n = 277) or 10-12 years (n = 292) after BC treatment at ages 40-50 years. Left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) were assessed by echocardiography. N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured in serum. Associations between patient-related and treatment-related risk factors and myocardial dysfunction were evaluated using linear and logistic regression. Median ages at BC diagnosis and cardiac assessment were 46.7 and 55.5 years, respectively. Anthracycline-treated patients (n = 313), compared to the no-anthracycline group (n = 256), more often had decreased LVEF (10% vs. 4%), impaired GLS (34% vs. 27%) and elevated NT-proBNP (23% vs. 8%). GLS and LVEF

declined in a linear fashion with increasing cumulative anthracycline dose (GLS: +0.23 and LVEF: -0.40 per cycle of 60 mg/m(2) ; P < 0.001) and GLS was worse for patients with left breast irradiation. The risk of NT-proBNP >125 ng/L was highest for patients who received 241-300 mg/m(2) anthracycline dose compared to the no-anthracycline group (odds ratio: 3.30, 95% confidence interval: 1.83-5.96).
Conclusion: Impaired GLS and increased NT-proBNP levels are present in a substantial proportion of young BC survivors treated with anthracyclines. Whether this will lead to future cardiac disease needs to be evaluated by longitudinal assessment.

Gepubliceerd: Eur J Heart Fail. 2020;22(2):338-46.
Impact factor: 11.627; Q1

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10. Three-year clinical outcome in all-comers with "silent" diabetes, prediabetes, or normoglycemia, treated with contemporary coronary drug-eluting stents: From the BIO-RESORT Silent Diabetes study
Ploumen EH, Buiten RA, Kok MM, Doggen CJM, van Houwelingen KG, Stoel MG, de Man F, Hartmann M, Zocca P, Linssen GCM, Doelman C, Kant GD, von Birgelen C.

Background: Patients with coronary disease may have unknown diabetes or prediabetes. We evaluated 3-year outcomes after percutaneous coronary intervention (PCI) with contemporary drug-eluting stents (DES) in patients with silent diabetes, prediabetes, and normoglycemia.
Methods: All BIO-RESORT trial (NCT01674803) participants without known diabetes, enrolled at our center, were invited for oral glucose tolerance testing (OGTT) and measurements of fasting plasma glucose and glycated hemoglobin (HbA1c).
Results: OGTT detected silent diabetes in 68 (6.9%), prediabetes in 132 (13.4%), and normoglycemia in 788 (79.8%) of all 988 study participants. Follow-up was available in 986 (99.8%) patients. The main endpoint target vessel failure (TVF: cardiac death, target vessel-related myocardial infarction [MI], or target vessel revascularization) differed between groups (14.8, 9.9, and 5.6%; p = .002), driven by MI during the first 48 hr and by cardiac death (p < .001; p = .026). Between 48 hr and 3-years, there was no significant between-group difference in TVF, target vessel MI, and target vessel revascularization. Multivariable analysis demonstrated that silent diabetes was independently associated with TVF (adjusted HR: 2.52, 95%-CI: 1.26-5.03). An alternative diagnostic approach-HbA1c and fasting plasma glucose-detected silent diabetes and prediabetes in 33 (3.3%) and 217 (22.0%) patients, and normoglycemia in 738 (74.7%); TVF rates were 12.1, 7.9, and 6.0% (p = .23).
Conclusion: In patients without known diabetes, abnormal glucose metabolism by OGTT was independently associated with higher 3-year TVF rates after PCI with contemporary DES. This difference was driven by periprocedural MI and cardiac death. After the first 48 hr, the rates of TVF, target vessel MI, and target vessel revascularization were low and did not differ significantly between metabolic groups.

Gepubliceerd: Catheter Cardiovasc Interv. 2020;96(2):E110-e8.
Impact factor: 2.044; Q3

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11. Healthcare Costs of Metastatic Cutaneous Melanoma in the Era of Immunotherapeutic and Targeted Drugs
Leeneman B, Uyl-de Groot CA, Aarts MJB, van Akkooi ACJ, van den Berkmortel F, van den Eertwegh AJM, de Groot JWB, Herbschleb KH, van der Hoeven JJM, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, Wouters M, Haanen J, Franken MG.

Immunotherapeutic and targeted drugs improved survival of patients with metastatic melanoma. There is, however, a lack of evidence regarding their healthcare costs in clinical practice. The aim of our study was to provide insight into real-world healthcare costs of patients with metastatic cutaneous melanoma. Data were obtained from the Dutch Melanoma Treatment Registry for patients who were registered between July 2012 and December 2018. Mean total/monthly costs per patient were reported for all patients, patients who did not receive systemic therapy, and patients who received systemic therapy. Furthermore, mean episode/monthly costs per line of therapy and drug were reported for patients who received systemic therapy. Mean total/monthly costs were euro 89,240/euro 6809: euro 7988/euro 2483 for patients who did not receive systemic therapy (n = 784) and euro 105,078/euro 7652 for patients who received systemic therapy (n = 4022). Mean episode/monthly costs were the highest for nivolumab plus ipilimumab (euro 79,675/euro 16,976), ipilimumab monotherapy (euro 79,110/euro 17,252), and dabrafenib plus trametinib (euro 77,053/euro 12,015). Dacarbazine yielded the lowest mean episode/monthly costs (euro 6564/euro 2027). Our study showed that immunotherapeutic and targeted drugs had a large impact on real-world healthcare costs. As new drugs continue entering the treatment landscape for (metastatic) melanoma, it remains crucial to monitor whether the benefits of these drugs outweigh their costs.

Gepubliceerd: Cancers (Basel). 2020;12(4).
Impact factor: 6.126; Q1

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12. Computed Tomography-Based Body Composition Is Not Consistently Associated with Outcome in Older Patients with Colorectal Cancer
Looijaard S, Meskers CGM, Slee-Valentijn MS, Bouman DE, Wymenga ANM, Klaase JM, Maier AB.

Background: Current literature is inconsistent in the associations between computed tomography (CT)-based body composition measures and adverse outcomes in older patients with colorectal cancer (CRC). Moreover, the associations with consecutive treatment modalities have not been studied. This study compared the associations of CT-based body composition measures with surgery- and chemotherapy-related complications and survival in older patients with CRC. MATERIALS AND
Methods: A retrospective single-center cohort study was conducted in patients with CRC aged ≥65 years who underwent elective surgery between 2010 and 2014. Gender-specific standardized scores of preoperative CT-based skeletal muscle (SM), muscle density, intermuscular adipose tissue (IMAT), visceral adipose tissue (VAT), subcutaneous adipose tissue, IMAT percentage, SM/VAT, and body mass index (BMI) were tested for their associations with severe postoperative complications, prolonged length of stay (LOS), readmission, and dose-limiting toxicity using logistic

regression and 1-year and long-term survival (range 3.7-6.6 years) using Cox regression. Bonferroni correction was applied to account for multiple testing.
Results: The study population consisted of 378 patients with CRC with a median age of 73.4 (interquartile range 69.5-78.4) years. Severe postoperative complications occurred in 13.0%, and 39.4% of patients died during follow-up. Dose-limiting toxicity occurred in 77.4% of patients receiving chemotherapy (n = 53). SM, muscle density, VAT, SM/VAT, and BMI were associated with surgery-related complications, and muscle density, IMAT, IMAT percentage, and SM/VAT were associated with long-term survival. After Bonferroni correction, no CT-based body composition measure was significantly associated with adverse outcomes. Higher BMI was associated with prolonged LOS.
Conclusion: The associations between CT-based body composition measures and adverse outcomes of consecutive treatment modalities in older patients with CRC were not consistent or statistically significant. IMPLICATIONS FOR PRACTICE: Computed tomography (CT)-based body composition, including muscle mass, muscle density, and intermuscular, visceral, and subcutaneous adipose tissue, showed inconsistent and nonsignificant associations with surgery-related complications, dose-limiting toxicity, and overall survival in older adults with colorectal cancer. This study underscores the need to verify whether CT-based body composition measures are worth implementing in clinical practice.

Gepubliceerd: Oncologist. 2020;25(3):e492-e501.
Impact factor: 5.025; Q2

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13. Impact of nationwide enhanced implementation of best practices in pancreatic cancer care (PACAP-1): a multicenter stepped-wedge cluster randomized controlled trial

Mackay TM, Smits FJ, Latenstein AEJ, Bogte A, Bonsing BA, Bos H, Bosscha K, Brosens LAA, Hol L, Busch ORC, Creemers GJ, Curvers WL, den Dulk M, van Dieren S, van Driel L, Festen S, van Geenen EJM, van der Geest LG, de Groot DJA, de Groot JWB, Haj Mohammad N, Haberkorn BCM, Haver JT, van der Harst E, Hemmink GJM, de Hingh IH, Hoge C, Homs MYV, van Huijgevoort NC, Jacobs M, Kerver ED, Liem MSL, Los M, Lubbinge H, Luelmo SAC, de Meijer VE, Mekenkamp L, Molenaar IQ, van Oijen MGH, Patijn GA, Quispel R, van Rijssen LB, Römkens TEH, van Santvoort HC, Schreinemakers JMJ, Schut H, Seerden T, Stommel MWJ, Ten Tije AJ, Venneman NG, Verdonk RC, Verheij J, van Vilsteren FGI, de Vos-Geelen J, Vulink A, Wientjes C, Wit F, Wessels FJ, Zonderhuis B, van Werkhoven CH, van Hooft JE, van Eijck CHJ, Wilmink JW, van Laarhoven HWM, Besselink MG.

Background: Pancreatic cancer has a very poor prognosis. Best practices for the use of chemotherapy, enzyme replacement therapy, and biliary drainage have been identified but their implementation in daily clinical practice is often suboptimal. We hypothesized that a nationwide program to enhance implementation of these best practices in pancreatic cancer care would improve survival and quality of life.
METHODS/
Design: PACAP-1 is a nationwide multicenter stepped-wedge cluster randomized controlled superiority trial. In a per-center stepwise and randomized manner, best practices in pancreatic cancer care regarding the use of (neo)adjuvant and palliative chemotherapy, pancreatic enzyme replacement therapy, and metal biliary stents are

implemented in all 17 Dutch pancreatic centers and their regional referral networks during a 6-week initiation period. Per pancreatic center, one multidisciplinary team functions as reference for the other centers in the network. Key best practices were identified from the literature, 3 years of data from existing nationwide registries within the Dutch Pancreatic Cancer Project (PACAP), and national expert meetings. The best practices follow the Dutch guideline on pancreatic cancer and the current state of the literature, and can be executed within daily clinical practice. The implementation process includes monitoring, return visits, and provider feedback in combination with education and reminders. Patient outcomes and compliance are monitored within the PACAP registries. Primary outcome is 1-year overall survival (for all disease stages). Secondary outcomes include quality of life, 3- and 5-year overall survival, and guideline compliance. An improvement of 10% in 1-year overall survival is considered clinically relevant. A 25-month study duration was chosen, which provides 80% statistical power for a mortality reduction of 10.0% in the 17 pancreatic cancer centers, with a required sample size of 2142 patients, corresponding to a 6.6% mortality reduction and 4769 patients nationwide.
Discussion: The PACAP-1 trial is designed to evaluate whether a nationwide program for enhanced implementation of best practices in pancreatic cancer care can improve 1-year overall survival and quality of life.
Trial registration: ClinicalTrials.gov, NCT03513705. Trial opened for accrual on 22th May 2018.

Gepubliceerd: Trials. 2020;21(1):334.
Impact factor: 1.883; Q3

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14. Generation and infusion of multi-antigen-specific T cells to prevent complications early after T-cell depleted allogeneic stem cell transplantation-a phase I/II study
Roex MCJ, van Balen P, Germeroth L, Hageman L, van Egmond E, Veld SAJ, Hoogstraten C, van Liempt E, Zwaginga JJ, de Wreede LC, Meij P, Vossen A, Danhof S, Einsele H, Schaafsma MR, Veelken H, Halkes CJM, Jedema I, Falkenburg JHF.

Prophylactic infusion of selected donor T cells can be an effective method to restore specific immunity after T-cell-depleted allogeneic stem cell transplantation (TCD-alloSCT). In this phase I/II study, we aimed to reduce the risk of viral complications and disease relapses by administrating donor-derived CD8(pos) T cells directed against cytomegalovirus (CMV), Epstein-Barr virus (EBV) and adenovirus antigens, tumor-associated antigens (TAA) and minor histocompatibility antigens (MiHA). Twenty-seven of thirty-six screened HLA-A*02:01(pos) patients and their CMV(pos) and/or EBV(pos) donors were included. Using MHC-I-Streptamers, 27 T-cell products were generated containing a median of 5.2 x 10(6) cells. Twenty-four products were administered without infusion-related complications at a median of 58 days post alloSCT. No patients developed graft-versus-host disease during follow-up. Five patients showed disease progression without coinciding expansion of TAA/MiHA-specific T cells. Eight patients experienced CMV- and/or EBV-reactivations. Four of these reactivations were clinically relevant requiring antiviral treatment, of which two progressed to viral disease. All resolved ultimately. In 2/4 patients with EBV-reactivations and 6/8 patients with CMV-reactivations, viral loads were followed by the expansion of donor-derived virus target-antigen-specific T cells. In conclusion,

generation of multi-antigen-specific T-cell products was feasible, infusions were well tolerated and expansion of target-antigen-specific T cells coinciding viral reactivations was illustrated in the majority of patients.

Gepubliceerd: Leukemia. 2020;34(3):831-44.
Impact factor: 8.665; Q1

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15. Proteomic markers with prognostic impact on outcome of chronic lymphocytic leukemia patients under chemo-immunotherapy: results from the HOVON 109 study
Saberi Hosnijeh F, van der Straten L, Kater AP, van Oers MHJ, Posthuma WFM, Chamuleau MED, Bellido M, Doorduijn JK, van Gelder M, Hoogendoorn M, de Boer F, Te Raa GD, Kerst JM, Marijt EWA, Raymakers RAP, Koene HR, Schaafsma MR, Dobber JA, Tonino SH, Kersting SS, Langerak AW, Levin MD.

Despite recent identification of several prognostic markers, there is still a need for new prognostic parameters able to predict clinical outcome in chronic lymphocytic leukemia (CLL) patients. Here, we aimed to validate the prognostic ability of known (proteomic) markers measured pretreatment and to search for new proteomic markers that might be related to treatment response in CLL. To this end, baseline serum samples of 51 CLL patients treated with chemo-immunotherapy were analyzed for 360 proteomic markers, using Olink technology. Median event-free survival (EFS) was 23 months (range: 1.25-60.9). Patients with high levels of sCD23 (>11.27, p=0.026), sCD27 (>11.03, p=0.04), SPINT1 (>1.6, p=0.001), and LY9 (>8.22, p=0.0003) had a shorter EFS than those with marker levels below the median. The effect of sCD23 on EFS differed between immunoglobulin heavy chain variable gene-mutated and unmutated patients, with the shortest EFS for unmutated CLL patients with sCD23 levels above the median. Taken together, our results validate the prognostic impact of sCD23 and highlight SPINT1 and LY9 as possible promising markers for treatment response in CLL patients.

Gepubliceerd: Exp Hematol. 2020;89:55-60 e6.
Impact factor: 2.820; Q3

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16. A man with painful shins
Snel FW, Kootstra GJ, Vonkeman HE.

A 55-year-old man was evaluated at the outpatient rheumatology clinic with painful shins since 6 weeks. He also had a maculopapular rash on his trunk. Bone scintigraphy showed bilateral tibia periostitis. Serologic testing for syphilis was positive matching active infection. The diagnosis secondary syphilis with bilateral tibia periostitis was made.

Gepubliceerd: Ned Tijdschr Geneeskd. 2020;164.
Impact factor: nvt; nvt

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17. High-Dose Chemotherapy With Hematopoietic Stem Cell Transplant in Patients With High-Risk Breast Cancer and 4 or More Involved Axillary Lymph Nodes: 20-Year Follow-up of a Phase 3 Randomized Clinical Trial
Steenbruggen TG, Steggink LC, Seynaeve CM, van der Hoeven JJM, Hooning MJ, Jager A, Konings IR, Kroep JR, Smit WM, Tjan-Heijnen VCG, van der Wall E, Bins AD, Linn SC, Schaapveld M, Jacobse JN, van Leeuwen FE, Schroder CP, van Tinteren H, de Vries EGE, Sonke GS, Gietema JA.

Importance: Trials of adjuvant high-dose chemotherapy (HDCT) have failed to show a survival benefit in unselected patients with breast cancer, but long-term follow-up is lacking. Objective: To determine 20-year efficacy and safety outcomes of a large trial of adjuvant HDCT vs conventional-dose chemotherapy (CDCT) for patients with stage III breast cancer.
Design, Setting, and Participants: This secondary analysis used data from a randomized phase 3 multicenter clinical trial of 885 women younger than 56 years with breast cancer and 4 or more involved axillary lymph nodes conducted from August 1, 1993, to July 31, 1999. Additional follow-up data were collected between June 1, 2016, and December 31, 2017, from medical records, general practitioners, the Dutch national statistical office, and nationwide cancer registries. Analysis was performed on an intention-to-treat basis. Statistical analysis was performed from February 1, 2018, to October 14, 2019.
Interventions: Participants were randomized 1:1 to receive 5 cycles of CDCT consisting of fluorouracil, 500 mg/m2, epirubicin, 90 mg/m2, and cyclophosphamide, 500 mg/m2, or HDCT in which the first 4 cycles were identical to CDCT and the fifth cycle was replaced by cyclophosphamide, 6000 mg/m2, thiotepa, 480 mg/m2, and carboplatin, 1600 mg/m2, followed by hematopoietic stem cell transplant.
Main Outcomes and Measures: Main end points were overall survival and safety and cumulative incidence risk of a second malignant neoplasm or cardiovascular events.
Results: Of the 885 women in the study (mean [SD] age, 44.5 [6.6] years), 442 were randomized to receive HDCT, and 443 were randomized to receive CDCT. With 20.4 years median follow-up (interquartile range, 19.2-22.0 years), the 20-year overall survival was 45.3% with HDCT and 41.5% with CDCT (hazard ratio, 0.89; 95% CI, 0.75-1.06). The absolute improvement in 20-year overall survival was 14.6% (hazard ratio, 0.72; 95% CI, 0.54-0.95) for patients with 10 or more invoved axillary lymph nodes and 15.4% (hazard ratio, 0.67; 95% CI, 0.42-1.05) for patients with triple-negative breast cancer. The cumulative incidence risk of a second malignant neoplasm at 20 years or major cardiovascular events was similar in both treatment groups (20-year cumulative incidence risk for second malignant neoplasm was 12.1% in the HDCT group vs 16.2% in the CDCT group, P = .10), although patients in the HDCT group more often had hypertension (21.7% vs 14.3%, P = .02), hypercholesterolemia (15.7% vs 10.6%, P = .04), and dysrhythmias (8.6% vs 4.6%, P = .005).
Conclusions and Relevance: High-dose chemotherapy provided no long-term survival benefit in unselected patients with stage III breast cancer but did provide improved overall survival in very high-risk patients (ie, with >/=10 involved axillary lymph nodes). High-dose chemotherapy did not affect long-term risk of a second malignant neoplasm or major cardiovascular events.
Trial Registration: ClinicalTrials.gov Identifier: NCT03087409.

Gepubliceerd: JAMA Oncol. 2020;6(4):528-34.
Impact factor: 24.799; Q1

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18. High-Dose Chemotherapy With Hematopoietic Stem Cell Transplant in Patients With High-Risk Breast Cancer-Reply
Steenbruggen TG, Steggink LC, Sonke GS.

Gepubliceerd: JAMA Oncol. 2020;6(8):1300.
Impact factor: 24.799; Q1

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19. Vascular aging in long-term survivors of testicular cancer more than 20 years after treatment with cisplatin-based chemotherapy
Stelwagen J, Lubberts S, Steggink LC, Steursma G, Kruyt LM, Donkerbroek JW, van Roon AM, van Gessel AI, van de Zande SC, Meijer C, Grafin Zu Eulenburg CH, Oosting SF, Nuver J, Walenkamp AME, Jan de Jong I, Lefrandt JD, Gietema JA.

Background: Late effects of cisplatin-based chemotherapy in testicular cancer survivors (TCS) include cardiovascular morbidity, but little data is available beyond 20 years. The objective was to assess vascular damage in very long-term TCS.
Methods: TCS (treated with chemotherapy or orchiectomy only) and age-matched healthy controls were invited. Study assessment included vascular stiffness with ultrasound measurement of carotid-femoral pulse wave velocity (cf-PWV).
Results: We included 127 TCS consisting of a chemotherapy group (70 patients) and an orchiectomy group (57 patients) along with 70 controls. Median follow-up was 28 years (range: 20-42). The cf-PWV (m/s) was higher in TCS than in controls (geometrical mean 8.05 (SD 1.23) vs. 7.60 (SD 1.21), p = 0.04). The cf-PWV was higher in the chemotherapy group than in the orchiectomy group (geometrical mean 8.39 (SD 1.22) vs. 7.61 (SD 1.21), p < 0.01). In the chemotherapy group cf-PWV increased more rapidly as a function of age compared to controls (regression coefficient b 7.59 x 10(-3) vs. 4.04 x 10(-3); p = 0.03).
Conclusion: Very long-term TCS treated with cisplatin-based chemotherapy show increased vascular damage compatible with "accelerated vascular aging" and continue to be at risk for cardiovascular morbidity, thus supporting the need for intensive cardiovascular risk management. CLINICAL
Trial registration: The clinical trial registration number is NCT02572934.

Gepubliceerd: Br J Cancer. 2020;123(11):1599-607.
Impact factor: 5.791; Q1

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20. Don't be guided purely by numbers: false increased TSH values due to analytical interference
Tibben NE, Bons JAP, van den Berg SAA, Huisman J, Krabbe JG.

Background: Physicians are often guided by laboratory values. When a clinical presentation does not match laboratory values, one must consider the possibility that these values may be falsely increased or decreased. A common cause is analytical interference.

Case Description: A 57-year-old male, presenting with fatigue and palpitations, had high TSH and normal FT4 values. Although there were no fitting clinical symptoms for these values, the patient was treated with levothyroxine assuming he had subclinical hypothyroidism. TSH levels remained high, however, whereas FT4 levels increased and the patient developed thyrotoxicosis. Eventually, it was discovered that the TSH was falsely elevated.
Conclusion: The patient turned out to have macro TSH, where TSH forms conjunctions with IgG into larger molecules. These conjugates cause a rarely occurring interference during laboratory analysis, resulting in a falsely increased TSH value.

Gepubliceerd: Ned Tijdschr Geneeskd. 2020;164.
Impact factor: nvt; nvt

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21. Age Does Matter in Adolescents and Young Adults versus Older Adults with Advanced Melanoma; A National Cohort Study Comparing Tumor Characteristics, Treatment Pattern, Toxicity and Response
van der Kooij MK, Wetzels M, Aarts MJB, van den Berkmortel F, Blank CU, Boers-Sonderen MJ, Dierselhuis MP, de Groot JWB, Hospers GAP, Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, Wouters M, Haanen J, van den Eertwegh AJM, Bastiaannet E, Kapiteijn E.

Cutaneous melanoma is a common type of cancer in Adolescents and Young Adults (AYAs, 15-39 years of age). However, AYAs are underrepresented in clinical trials investigating new therapies and the outcomes from these therapies for AYAs are therefore unclear. Using prospectively collected nation-wide data from the Dutch Melanoma Treatment Registry (DMTR), we compared baseline characteristics, mutational profiles, treatment strategies, grade 3-4 adverse events (AEs), responses and outcomes in AYAs (n = 210) and older adults (n = 3775) who were diagnosed with advanced melanoma between July 2013 and July 2018. Compared to older adults, AYAs were more frequently female (51% versus 40%, p = 0.001), and had a better Eastern Cooperative Oncology Group performance status (ECOG 0 in 54% versus 45%, p = 0.004). BRAF and NRAS mutations were age dependent, with more BRAF V600 mutations in AYAs (68% versus 46%) and more NRAS mutations in older adults (13% versus 21%), p < 0.001. This finding translated in distinct first-line treatment patterns, where AYAs received more initial targeted therapy. Overall, grade 3-4 AE percentages following first-line systemic treatment were similar for AYAs and older adults; anti-PD-1 (7% versus 14%, p = 0.25), anti-CTLA-4 (16% versus 33%, p = 0.12), anti-PD-1 + anti-CTLA-4 (67% versus 56%, p = 0.34) and BRAF/MEK-inhibition (14% versus 23%, p = 0.06). Following anti-CTLA-4 treatment, no AYAs experienced a grade 3-4 colitis, while 17% of the older adults did (p = 0.046). There was no difference in response to treatment between AYAs and older adults. The longer overall survival observed in AYAs (hazard ratio (HR) 0.7; 95% CI 0.6-0.8) was explained by the increased cumulative incidence of non-melanoma related deaths in older adults (sub-distribution HR 2.8; 95% CI 1.5-4.9), calculated by competing risk analysis. The results of our national cohort study show that baseline characteristics and mutational profiles differ between AYAs and older adults with advanced melanoma, leading to different treatment choices made in daily practice. Once

treatment is initiated, AYAs and older adults show similar tumor responses and melanoma-specific survival.

Gepubliceerd: Cancers (Basel). 2020;12(8).
Impact factor: 6.126; Q1

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22. Survival outcomes of patients with advanced mucosal melanoma diagnosed from 2013 to 2017 in the Netherlands - A nationwide population-based study
van Zeijl MCT, Boer FL, van Poelgeest MIE, van den Eertwegh AJM, Wouters M, de Wreede LC, Aarts MJB, van den Berkmortel F, de Groot JWB, Hospers GAP, Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, Boers-Sonderen MJ, Kapiteijn EHW, Haanen J.

Background: Mucosal melanoma (MM) is rare and has a poor prognosis. Since 2011, new effective treatments are available for advanced melanoma. It is unclear whether patients with mucosal melanoma equally benefit from these new treatments compared with patients with cutaneous melanoma (CM).
Methods: Patients with advanced MM and CM diagnosed between 2013 and 2017 were included from a nationwide population-based registry - the Dutch Melanoma Treatment Registry. Overall survival (OS) was estimated with the Kaplan-Meier method (also for a propensity score-matched cohort). A Cox model was used to analyse the association of possible prognostic factors with OS.
Results: In total, 120 patients with MM and 2960 patients with CM were included. Median OS was 8.7 months and 14.5 months, respectively. Patients with MM were older (median age 70 versus 65 years) and more often female (60% versus 41%), compared with CM. In total, 77% and 2% of the MM patients were treated with first-line immunotherapy and targeted therapy, respectively, compared with 49% and 33% of the CM patients. In contrast to CM, OS for MM did not improve for patients diagnosed in 2015-2017, compared with 2013-2014. ECOG performance score >/=1 (HR = 1.99 [1.26-3.15; p = 0.003]) and elevated LDH level (HR = 1.63 [0.96-2.76]; p = 0.069) in MM were associated with worse survival.
Conclusions: Within the era of immune and targeted therapies, prognosis for patients with advanced MM has not improved as much as for CM. Collaboration is necessary to enlarge sample size for research to improve immunotherapeutic strategies and identify targetable mutations.

Gepubliceerd: Eur J Cancer. 2020;137:127-35.
Impact factor: 7.275; Q1

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23. Real-world Outcomes of First-line Anti-PD-1 Therapy for Advanced Melanoma: A Nationwide Population-based Study
van Zeijl MCT, Haanen J, Wouters M, de Wreede LC, Jochems A, Aarts MJB, van den Berkmortel F, de Groot JWB, Hospers GAP, Kapiteijn EW, Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, van der Hoeven KJM, van den Eertwegh AJM.

The efficacy of anti-programmed death-1 (PD-1) monotherapy for advanced melanoma has been established, but it is unknown to what extent patients benefit in

the real world. In this observational study with nationwide population-based data from the Dutch Melanoma Treatment Registry, we analyzed real-world outcomes of first-line anti-PD-1 monotherapy in advanced melanoma patients diagnosed in 2015 to 2016. Overall survival (OS) was estimated with the Kaplan-Meier method. Competing risks analysis was used to estimate probabilities for second-line treatment, with death as competing risk. With a Cox model, the association of factors with OS was estimated. Patients who received anti-PD-1 monotherapy (n=550) had a median age of 65 years and 502 (95%) patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1, 383 (70%) had normal lactate dehydrogenase (LDH), 370 (67%) had stage IV-M1c disease, and in 441 (81%), brain metastases were absent. The median OS was 24 months [95% confidence interval (CI): 20-30 mo]. The median OS of patients normally eligible for phase III trial participation was 31 months (95% CI: 23-not estimable). The BRAF mutation was associated with superior OS. ECOG PS of >/=1, symptomatic brain metastases, and liver metastases were associated with inferior OS and, together with elevated LDH, with death before second-line treatment. Patients with a complete response had a 2-year OS probability from first reported complete response of 92% (95% CI: 86%-99%). Real-world advanced melanoma patients in the Netherlands have benefitted from anti-PD-1 monotherapy. ECOG PS >/=1, symptomatic brain metastasis, liver metastasis, and elevated LDH are important prognostic factors for survival. The additional information that this study provides could help to improve more effective use in the real world.

Gepubliceerd: J Immunother. 2020;43(8):256-64.
Impact factor: 4.110; Q2

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24. Real-world outcomes of advanced melanoma patients not represented in phase III trials

van Zeijl MCT, Ismail RK, de Wreede LC, van den Eertwegh AJM, de Boer A, van Dartel M, Hilarius DL, Aarts MJB, van den Berkmortel F, Boers-Sonderen MJ, de Groot JB, Hospers GAP, Kapiteijn E, Piersma D, van Rijn RS, Suijkerbuijk KPM, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, Haanen J, Wouters M.

The aim was to provide evidence on systemically treated patients with advanced melanoma not represented in phase III trials to support clinical decision-making. Analysis were performed on advanced melanoma patients diagnosed between 2014 and 2017 in the Netherlands, treated with immune- or targeted therapy, who met >/=1 trial exclusion criteria. These criteria were derived from the KEYNOTE-006 and CHECKMATE-067/-066 phase III trials. Prognostic importance of factors associated with overall survival (OS) was assessed with the Kaplan-Meier method, Cox models, predicted OS probabilities of prognostic subgroups and a conditional inference survival tree (CIST). A nationwide population-based registry was used as data source. Of 2536 systemically treated patients with advanced melanoma, 1004 (40%) patients were ineligible for phase IIII trials. Ineligible patients had a poorer median OS (mOS) compared to eligible patients (8.8 vs 23 months). Eligibility criteria strongly associated with OS in systemically treated ineligible patients were Eastern Cooperative Oncology Group Performance Score (ECOG PS) >/=2, brain metastases (BM) and lactate dehydrogenase (LDH) of >500 U/L. Patients with ECOG PS of >/=2 with or without symptomatic BM had a predicted mOS of 6.5 and 11.3 months and a 3-year survival probability of 9.3% and 23.6%, respectively. The CIST showed the

strongest prognostic covariate for survival was LDH, followed by ECOG PS. The prognosis of patients with LDH of >500 U/L is poor, but long-term survival is possible. The prognosis of ineligible patients with advanced melanoma in real-world was very heterogeneous and highly dependent on LDH value, ECOG PS and symptomatic BM.

Gepubliceerd: Int J Cancer. 2020;147(12):3461-70.
Impact factor: 5.145; Q1

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25. Association of Anti-TNF with Decreased Survival in Steroid Refractory Ipilimumab and Anti-PD1-Treated Patients in the Dutch Melanoma Treatment Registry
Verheijden RJ, May AM, Blank CU, Aarts MJB, van den Berkmortel F, van den Eertwegh AJM, de Groot JWB, Boers-Sonderen MJ, van der Hoeven JJM, Hospers GA, Piersma D, van Rijn RS, Ten Tije AJ, van der Veldt AAM, Vreugdenhil G, van Zeijl MCT, Wouters M, Haanen J, Kapiteijn E, Suijkerbuijk KPM.

Purpose: Unleashing the immune system by PD-1 and/or CTLA-4 blockade can cause severe immune-related toxicity necessitating immunosuppressive treatment. Whether immunosuppression for toxicity impacts survival is largely unknown.
EXPERIMENTAL
Design: Using data from the prospective nationwide Dutch Melanoma Treatment Registry (DMTR), we analyzed the association between severe toxicity and overall survival (OS) in 1,250 patients with advanced melanoma who were treated with immune checkpoint inhibitors (ICI) in first line between 2012 and 2017. Furthermore, we analyzed whether toxicity management affected survival in these patients.
Results: A total of 1,250 patients were included, of whom 589 received anti-PD1 monotherapy, 576 ipilimumab, and 85 combination therapy. A total of 312 patients (25%) developed severe (grade >/=3) toxicity. Patients experiencing severe ICI toxicity had a significantly prolonged survival with a median OS of 23 months compared with 15 months for patients without severe toxicity [hazard ratio (HRadj) = 0.77; 95% confidence interval (CI), 0.63-0.93]. Among patients experiencing severe toxicity, survival was significantly decreased in patients who received anti-TNF +/- steroids for steroid-refractory toxicity compared with patients who were managed with steroids only (HRadj = 1.61; 95% CI, 1.03-2.51), with a median OS of 17 and 27 months, respectively.
Conclusions: Patients experiencing severe ICI toxicity have a prolonged OS. However, this survival advantage is abrogated when anti-TNF is administered for steroid-refractory toxicity. Further prospective studies are needed to assess the effect of different immunosuppressive regimens on checkpoint inhibitor efficacy.See related commentary by Weber and Postow, p. 2085.

Gepubliceerd: Clin Cancer Res. 2020;26(9):2268-74.
Impact factor: 10.107; Q1

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26. Lower risk of severe checkpoint inhibitor toxicity in more advanced disease
Verheijden RJ, May AM, Blank CU, van der Veldt AAM, Boers-Sonderen MJ, Aarts MJB, van den Berkmortel F, van den Eertwegh AJM, de Groot JWB, van der Hoeven

JJM, Hospers GAP, Piersma D, van Rijn RS, Ten Tije AJ, Vreugdenhil G, van Zeijl MCT, Wouters M, Haanen J, Kapiteijn E, Suijkerbuijk KPM.

Background: Immune checkpoint inhibitor (ICI) can cause severe and sometimes fatal immune-related adverse events (irAEs). Since these irAEs mimick immunological disease, a female predominance has been speculated on. Nevertheless, no demographic or tumour-related factors associated with an increased risk of irAEs have been identified until now.
Methods: Risk ratios of severe (grade >/=3) irAEs for age, sex, WHO performance status, number of comorbidities, stage of disease, number of metastases and serum lactate dehydrogenases (LDH) were estimated using data from anti-PD1-treated patients with advanced melanoma in the prospective nationwide Dutch Melanoma Treatment Registry.
Results: 111 (11%) out of 819 anti-programmed cell death 1 treated patients experienced severe irAEs. Patients with non-lung visceral metastases (stage IV M1c or higher) less often experienced severe irAEs (11%) compared with patients with only lung and/or lymph node/soft tissue involvement (stage IV M1b or lower; 19%; adjusted risk ratio (RRadj) 0.63; 95% CI 0.41 to 0.94). Patients with LDH of more than two times upper limit of normal had a non-significantly lower risk of developing severe irAEs than those with normal LDH (RRadj 0.65; 95% CI 0.20 to 2.13). None of the other variables were associated with severe irAEs.
Conclusion: In patients with melanoma, more advanced disease is associated with a lower rate of severe irAEs. No association with sex was found.

Gepubliceerd: ESMO Open. 2020;5(6):e000945.
Impact factor: 5.329; Q1

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27. 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). 2020;29(1):e13185.
Impact factor: 2.161; Q1

Totale impact factor: 169.005
Gemiddelde impact factor: 6.259

Aantal artikelen 1e, 2e of laatste auteur: 6
Totale impact factor: 63.386
Gemiddelde impact factor: 10.564

Kaakchirurgie

1. Swollen left eye, day after an elective shoulder-MRI
van Zandwijk JK, Kolenaar B, van Blommestein R.

A 63-year-old male checked in 2 days after he had a shoulder MRI with complaints of a swollen and painful left eye. An anteroposterior X-ray of the orbit showed a foreign body of approximately 2.5 cm in de left maxillary sinus and orbit. 11 years ago, patient built a barn using an automatic staple-gun. He recalls having a little wound on his left cheek. His medical history showed that the man had undergone an MRI for his knee 3 years earlier and another for prostate complaints a year ago. Exact localization of the foreign body was confirmed by a CT scan of the orbit. The extraction of the foreign body has been performed by a combined approach, nasal by the otorhinolaryngologist and orbital by the oral and maxillofacial surgeon. This is the first case report on orbital penetration of a luxated foreign body after 3 elective MRI's.

Gepubliceerd: Ned Tijdschr Tandheelkd. 2020;127(9):481-6.
Impact factor: nvt; nvt

Totale impact factor: 0
Gemiddelde impact factor: 0

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

Kindergeneeskunde

1. Prescribed Protein Intake Does Not Meet Recommended Intake in Moderate- and Late-Preterm Infants: Contribution to Weight Gain and Head Growth
Gerritsen L, Lindeboom R, Hummel T.

Background: The purpose of the study was to evaluate differences between prescribed and recommended protein intake in moderate-preterm (MP) and late-preterm (LP) infants and examine the contribution of the first week's prescribed protein intake to growth until term age.
Methods: Data on intake and anthropometrics were collected retrospectively in 235 preterm infants admitted to our general hospital's neonatal ward: 60 MP (32(0/7) - 33(6/7) weeks' gestational age) and 175 LP (34(0/7) -36(6/7) weeks' gestational age). Differences between prescribed and recommended protein intake during the first postnatal week and z-score change for weight and head circumference (HC) between birth and term age were calculated. Multiple regression was used to evaluate the independent contribution of first week's prescribed protein intake to growth until term age.
Results: At day 7, 58% of MP and 19% of LP infants reached recommended protein intake. At term age, mean z-score change was -0.4 for weight and +0.1 for HC. Mean protein intake (g/kg/d) was associated with z-score change of +0.34 (95% CI, 0.14-0.53; P < .001) for weight and +0.25 (95% CI, 0-0.5; P = .03) for HC. Reaching recommended protein intake at day 7 was only independently associated with weight z-score change (+0.22 [95% CI, 0.04-0.41; P = .002]).
Conclusion: First week's prescribed protein intake does not meet recommended intake. Higher protein intakes in the first postnatal week result in increased weight gain and head growth until term age. Desirability and feasibility of increasing the protein intake need careful consideration and further discussion.

Gepubliceerd: Nutr Clin Pract. 2020;35(4):729-37.
Impact factor: 2.573; Q3

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2. Assessing paediatric exercise-induced bronchoconstriction using electromyography
Keijzer PB, van der Kamp MR, Thio BJ, de Jongh FHC, Driessen JMM.

Background: Asthma is one of the most common chronic diseases in childhood, occurring in up to 10% of all children. Exercise-induced bronchoconstriction (EIB) is indicative of uncontrolled asthma and can be assessed using an exercise challenge test (ECT). However, this test requires children to undergo demanding repetitive forced breathing manoeuvres. We aimed to study the electrical activity of the diaphragm using surface electromyography (EMG) as an alternative measure to assess EIB.
Methods: Forty-two children suspected of EIB performed an ECT wearing a portable EMG amplifier. EIB was defined as a fall in FEV 1 of more than 13%. Children performed spirometry before exercise, and at 1, 3 and 6 min after exercise until the nadir FEV1 was attained and after the use of a bronchodilator. EMG measurements were obtained between spirometry measurements.

Results: Twenty out of 42 children were diagnosed with EIB. EMG peak amplitudes measured at the diaphragm increased significantly more in children with EIB; 4.85 muV (1.82-7.84), compared to children without EIB; 0.20 muV (-0.10-0.54), ($p<0.001$) at the lowest FEV 1 post-exercise. Furthermore, the increase in EMG peak amplitude could accurately distinguish between EIB and non-EIB using a cut-off of 1.15 muV (sensitivity 95%, specificity 91%).
Conclusion: EMG measurements of the diaphragm are strongly related to the FEV1 and can accurately identify EIB. EMG measurements are a less invasive, effort-independent measure to assess EIB and could be an alternative when spirometry is not feasible.

Gepubliceerd: ERJ Open Res. 2020;6(2):00298-2019.
Impact factor: nvt; nvt

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3. Can Pediatricians Assess Exercise-Induced Bronchoconstriction From Post-exercise Videos?
Lammers N, van Hoesel MHT, Brusse-Keizer MGJ, van der Palen J, Spenkelink-Visser R, Driessen JMM, Thio BJ.

Objective: Exercise-induced bronchoconstriction (EIB) is a highly prevalent morbidity of childhood asthma and defined by a transient narrowing of the airways during or after physical exercise. An exercise challenge test (ECT) is the reference standard for the diagnosis of EIB. Video evaluation of EIB symptoms could be a practical alternative for the assessment of EIB. We studied the ability of pediatricians to assess EIB from post-exercise videos.
Methods: A clinical assessment was performed in 20 asthmatic children (mean age 11.6 years) and EIB was measured with a standardized ECT performed in cold, dry air. EIB was defined as a fall in forced expiratory volume in 1 s (FEV(1)) of ≥10% post-exercise. Children were filmed before and after exercise in frontal position and bare chested. The clinical assessment results and videos were shown to 20 pediatricians (mean experience 14.4 years). Each assessed EIB severity in 5 random children providing 100 assessments, scored on a continuous rating scale (0-10) and in severity classifications (no, mild, moderate, severe) using a scoring list including physical asthma symptoms. Correlations between predicted scores and objective scores were calculated with Spearman's rho and Cohen's Kappa. A generalized linear model was used to assess the relationship between physical symptoms and fall in FEV(1).
Results: Median fall in FEV(1) after exercise was 15.1% (IQR 1.2-65.1). Pediatricians detected EIB with a sensitivity of 78% (95% CI 66-87%) and a specificity of 40% (95% CI 27-55%). The positive predictive value for a pediatricians' diagnosis of EIB was 61% (95% CI 50-72%). The negative predictive value was 60% (95% CI 42-76%). The agreement between predicted EIB severity classifications and the validated classifications based on the ECT's, was fair [Kappa = 0.36 (95% CI 0.23-0.48)]. The correlation between predicted EIB severity scored on a continuous rating scale and fall in FEV(1) after exercise was weak ($r(s) = 0.39$, $p < 0.001$). Independent predictive variables for fall in FEV(1) were wheezing (-11%), supraclavicular retractions (-8.4%) and a prolonged expiratory phase (-8.8%).

Conclusion: The ability of pediatricians to assess EIB from post-exercise videos is fair at best, implicating that standardized ECT's are still vital in the assessment of EIB.

Gepubliceerd: Front Pediatr. 2020;7:561.
Impact factor: 2.634; Q1

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4. The Visual Analog Scale detects exercise-induced bronchoconstriction in children with asthma
Lammers N, van Hoesel MHT, van der Kamp M, Brusse-Keizer M, van der Palen J, Visser R, Driessen JMM, Thio BJ.

Objective: Exercise-induced bronchoconstriction (EIB) is a specific morbidity of childhood asthma and an important sign of uncontrolled asthma. The occurrence of EIB is insufficiently identified by the Childhood Asthma Control Test (C-ACT) and Asthma Control Test (ACT). This study aimed to (1) evaluate the Visual Analog Scale (VAS) for dyspnea as a tool to detect EIB in asthmatic children and (2) assess the value of combining (C-)ACT outcomes with VAS scores.
Methods: We measured EIB in 75 asthmatic children (mean age 10.8 years) with a standardized exercise challenge test (ECT) performed in cold and dry air. Children and parents reported VAS dyspnea scores before and after the ECT. Asthma control was assessed by the (C-)ACT.
Results: Changes in VAS scores (ΔVAS) of children and parents correlated moderately with fall in forced expiratory volume in 1 second (FEV(1)), respectively $r(s)=0.57$ ($p < .001$) and $r(s)=0.58$ ($p < .001$). At a ΔVAS cutoff value of ≥3 in children, sensitivity and specificity for EIB were 80% and 79% (AUC 0.82). Out of 38 children diagnosed with EIB, 37 had a (C-)ACT score of ≤19 and/or a ΔVAS of ≥3, corresponding with a sensitivity of 97% and a negative predictive value of 96%.
Conclusion: This study shows that the VAS could be an effective additional tool for diagnosing EIB in children. A reported difference in VAS scores of ≥3 after a standardized ECT combined with low (C-)ACT scores was highly effective in detecting and excluding EIB.

Gepubliceerd: J Asthma. 2020;57(12):1347-53.
Impact factor: 1.899; Q3

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5. Does immediate smart feedback on therapy adherence and inhalation technique improve asthma control in children with uncontrolled asthma? A study protocol of the IMAGINE I study
Sportel ET, Oude Wolcherink MJ, van der Palen J, Lenferink A, Thio BJ, Movig KLL, Brusse-Keizer MGJ.

Background: Many asthmatic children suffer from uncontrolled asthma with frequent exacerbations, despite an optimal treatment plan using inhalation medication. Studies have shown that therapy adherence and inhalation technique are often suboptimal in asthmatic children, but these have traditionally been hard to measure. A novel device functioning as an add-on to the inhaler has been developed to measure both aspects by recording vibration patterns during inhalation. This data can be converted to smart

feedback and provided to patients immediately via a mobile application. The aim of this study is to improve asthma control in children between 6 and 18 years old by providing immediate smart feedback on the intake of inhalation medication. Asthma control will be measured by forced expiratory volume in 1 s, (Childhood) Asthma Control Test ((c-)ACT) score, and lung function variability and reversibility.
Methods: The study will be performed in Medisch Spectrum Twente (Enschede, The Netherlands). The goal is to include 68 uncontrolled moderate to severe asthmatic children between 6 and 18 years old who receive controller inhalation medication through the Nexthaler®, Ellipta®, or Spiromax®. The study consists of three phases. Phase 1 is observational and will last 4 weeks to observe the baseline adherence and inhalation technique as monitored by the add-on device. A randomised controlled trial lasting 6 weeks will be performed in phase 2. Patients in the intervention group will receive immediate smart feedback about the performed inhalations via a mobile application. In the control group, adherence and inhalation technique will be monitored, but patients will not receive feedback. In phase 3, also lasting 6 weeks, the feedback will be ceased for all children and revision of current therapy may occur, depending on the findings in phase 2. Asthma control can be assessed by means of spirometry (both at home and in the hospital) and (c-)ACT questionnaires.
Discussion: Immediate smart feedback may improve therapy adherence and inhalation technique, and thus asthma control in children and prevent unnecessary switches to targeted biologics. Performing this study in children is desired, since they are known to react differently to feedback and medication than adults.
Trial registration: Dutch Trial Register NL7705 . Registered on 29 April 2019.

Gepubliceerd: Trials. 2020;21(1):801.
Impact factor: 1.883; Q3

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6. Test Strategies to Predict Inflammatory Bowel Disease Among Children With Nonbloody Diarrhea
Van de Vijver E, Heida A, Ioannou S, Van Biervliet S, Hummel T, Yuksel Z, Gonera-de Jong G, Schulenberg R, Muller Kobold A, Verkade HJ, van Rheenen PF.

Objectives: We evaluated 4 diagnostic strategies to predict the presence of inflammatory bowel disease (IBD) in children who present with chronic nonbloody diarrhea and abdominal pain.
Methods: We conducted a prospective cohort study including 193 patients aged 6 to 18 years who underwent a standardized diagnostic workup in secondary or tertiary care hospitals. Each patient was assessed for symptoms, C-reactive protein (>10 mg/L), hemoglobin (<-2 SD for age and sex), and fecal calprotectin (≥250 µg/g). Patients with rectal bleeding or perianal disease were excluded because the presence of these findings prompted endoscopy regardless of their biomarkers. Primary outcome was IBD confirmed by endoscopy or IBD ruled out by endoscopy or uneventful clinical follow-up for 6 months.
Results: Twenty-two of 193 (11%) children had IBD. The basic prediction model was based on symptoms only. Adding blood or stool markers increased the AUC from 0.718 (95% confidence interval [CI]: 0.604-0.832) to 0.930 (95% CI: 0.884-0.977) and 0.967 (95% CI: 0.945-0.990). Combining symptoms with blood and stool markers outperformed all other strategies (AUC 0.997 [95% CI: 0.993-1.000]). Triaging with a strategy that involves symptoms, blood markers, and calprotectin will result in 14 of

100 patients being exposed to endoscopy. Three of them will not have IBD, and no IBD-affected child will be missed.
Conclusions: Evaluating symptoms plus blood and stool markers in patients with nonbloody diarrhea is the optimal test strategy that allows pediatricians to reserve a diagnostic endoscopy for children at high risk for IBD.

Gepubliceerd: Pediatrics. 2020;146(2).
Impact factor: 5.359; Q1

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7. Influence of Dietary Advice Including Green Vegetables, Beef, and Whole Dairy Products on Recurrent Upper Respiratory Tract Infections in Children: A Randomized Controlled Trial
van der Gaag E, Brandsema R, Nobbenhuis R, van der Palen J, Hummel T.

Background: Since no treatment exists for children suffering from upper respiratory tract infections (URTIs) without immunological disorders, we searched for a possible tool to improve the health of these children. AIM: We evaluated whether dietary advice (based on food matrix and food synergy), including standard supportive care, can decrease the number and duration of URTIs in children with recurrent URTIs.
Design and Setting: This study was a multicenter randomized controlled trial in two pediatric outpatient clinics in the Netherlands, with 118 children aged one to four years with recurrent URTIs. The dietary advice group received dietary advice plus standard supportive care, while the control group received standard supportive care alone for six months. The dietary advice consisted of green vegetables five times per week, beef three times per week, 300 mL whole milk per day, and whole dairy butter on bread every day. Portion sizes were age-appropriate.
Results and Conclusion: Children in the dietary advice group had 4.8 (1.6-9.5) days per month with symptoms of an URTI in the last three months of the study, compared to 7.7 (4.0-12.3) in the control group ($p = 0.028$). The total number of URTIs during the six-month study period was 5.7 (0.55) versus 6.8 (0.49), respectively ($p = 0.068$). The use of antibiotics was significantly reduced in the dietary advice group, as well as visits to a general practitioner, thereby possibly reducing healthcare costs. The results show a reduced number of days with symptoms of a URTI following dietary advice. The number of infections was not significantly reduced.

Gepubliceerd: Nutrients. 2020;12(1).
Impact factor: 4.546; Q1

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8. A Lifestyle (Dietary) Intervention Reduces Tiredness in Children with Subclinical Hypothyroidism, a Randomized Controlled Trial
van der Gaag E, van der Palen J, Schaap P, van Voorthuizen M, Hummel T.

Background: Subclinical hypothyroidism (SH) in children and adults is a subject for discussion in terms of whether to treat it or not with respect to the short-term clinical implications and consequences of SH and in the long term. If treatment with thyroxine supplementation is not indicated, no other treatment is available. We investigated whether a lifestyle (dietary) intervention improves or normalizes SH or decreases the presence of Thyroid Stimulating Hormone (TSH) and/or tiredness.

Methods: We randomized children aged 1-12 years with SH to the control group (standard care = no treatment) or intervention group (dietary intervention). The dietary intervention consisted of green vegetables, beef, whole milk and butter for 6 months. The rest of the diet remained unchanged. We measured TSH, FreeT4, Lipid profile, Body Mass Index (BMI) and Pediatric Quality of Life (PedQL) multidimensional fatigue scale scores.
Results: In total, 62 children were included. After 6 months, TSH decreased in both groups without a significant difference between the groups (p = 0.98). PedQL fatigue scores for sleep (p = 0.032) and total fatigue scores (p = 0.039) improved significantly in the intervention group, compared to the control group. No unfavorable effects occurred in the lipid profile or BMI.
Conclusion: The lifestyle (dietary) intervention did not normalize SH and TSH levels, but it significantly reduced tiredness. These results suggest that children's well-being can be improved without medication.

Gepubliceerd: Int J Environ Res Public Health. 2020;17(10).
Impact factor: 2.468; Q2

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9. WEARCON: wearable home monitoring in children with asthma reveals a strong association with hospital based assessment of asthma control
van der Kamp MR, Klaver EC, Thio BJ, Driessen JMM, de Jongh FHC, Tabak M, van der Palen J, Hermens HJ.

Background: Asthma is one of the most common chronic diseases in childhood. Regular follow-up of physiological parameters in the home setting, in relation to asthma symptoms, can provide complementary quantitative insights into the dynamics of the asthma status. Despite considerable interest in asthma home-monitoring in children, there is a paucity of scientific evidence, especially on multi-parameter monitoring approaches. Therefore, the aim of this study is to investigate whether asthma control can be accurately assessed in the home situation by combining parameters from respiratory physiology sensors.
Methods: Sixty asthmatic and thirty non-asthmatic children were enrolled in the observational WEARCON-study. Asthma control was assessed according to GINA guidelines by the paediatrician. All children were also evaluated during a 2-week home-monitoring period with wearable devices; a physical activity tracker, a handheld spirometer, smart inhalers, and an ambulatory electrocardiography device to monitor heart and respiratory rate. Multiple logistic regression analysis was used to determine which diagnostic measures were associated with asthma control.
Results: 24 of the 27 uncontrolled asthmatic children and 29 of the 32 controlled asthmatic children could be accurately identified with this model. The final model showed that a larger variation in pre-exercise lung function (OR = 1.34 95%-CI 1.07-1.68), an earlier wake-up-time (OR = 1.05 95%-CI 1.01-1.10), more reliever use (OR = 1.11 95%-CI 1.03-1.19) and a longer respiratory rate recovery time (OR = 1.12 95%-CI 1.05-1.20) were significant contributors to the probability of having uncontrolled asthma.
Conclusions: Home-monitoring of physiological parameters correlates with paediatrician assessed asthma control. The constructed multivariate model identifies 88.9% of all uncontrolled asthmatic children, indicating a high potential for monitoring

of asthma control. This may allow healthcare professionals to assess asthma control at home.
Trial registration: Netherlands Trail Register, NL6087 . Registered 14 February 2017.

Gepubliceerd: BMC Med Inform Decis Mak. 2020;20(1):192.
Impact factor: 2.317; Q3

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10. COVID-19: Technology-Supported Remote Assessment of Pediatric Asthma at Home
van der Kamp MR, Tabak M, de Rooij S, van Lierop PPE, Thio BJ.

The COVID-19 crisis has pressured hospital-based care for children with high-risk asthma as they have become deprived of regular clinical evaluations. However, COVID-19 also provided important lessons about implementing novel directions for care. Personalized eHealth technology, tailored to the individual and the healthcare system, could substitute elements of hospital care and facilitate early and appropriate medical anticipation in response to imminent loss of control. This perspective article discusses new approaches to the clinical, organizational, and scientific aspects of the use of eHealth technology in pediatric asthma care in times of COVID-19, as illustrated by a case report of an acute asthma exacerbation possibly caused by COVID-19 infection.

Gepubliceerd: Front Pediatr. 2020;8:529.
Impact factor: 2.634; Q1

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11. 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. 2020;24(4):577-88.

Impact factor: 1.368; Q3

Totale impact factor: 27.681
Gemiddelde impact factor: 2.516

Aantal artikelen 1e, 2e of laatste auteur: 9
Totale impact factor: 20.439
Gemiddelde impact factor: 2.271

Klinische chemie

1. A new gene associated with a beta-thalassemia phenotype: the observation of variants in SUPT5H
Achour A, Koopmann T, Castel R, Santen GWE, den Hollander N, Knijnenburg J, Ruivenkamp CAL, Arkesteijn SGJ, Ter Huurne J, Bisoen S, Verschuren M, Vijfhuizen L, Schaap R, Grimbergen A, Slomp J, Traeger-Synodinos J, Vrettou C, Pissard S, Galacteros F, Baas F, Harteveld CL.

Gepubliceerd: Blood. 2020;136(15):1789-93.
Impact factor: 17.794; Q1

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2. Lifestyle-Related Exposure to Cadmium and Lead is Associated with Diabetic Kidney Disease
Hagedoorn IJM, Gant CM, Huizen SV, Maatman R, Navis G, Bakker SJL, Laverman GD.

Background: Environmental factors contributing to diabetic kidney disease are incompletely understood. We investigated whether blood cadmium and lead concentrations were associated with the prevalence of diabetic kidney disease, and to what extent lifestyle-related exposures (diet and smoking) contribute to blood cadmium and lead concentrations. MATERIAL AND
Methods: In a cross-sectional analysis in 231 patients with type 2 diabetes included in the DIAbetes and LifEstyle Cohort Twente (DIALECT-1), blood cadmium and lead concentrations were determined using inductively coupled plasma mass spectrometry. The associations between diet (derived from food frequency questionnaire), smoking and cadmium and lead were determined using multivariate linear regression. The associations between cadmium and lead and diabetic kidney disease (albumin excretion >30 mg/24 h and/or creatinine clearance <60 mL/min/1.73 m(2)) were determined using multivariate logistic regression.
Results: Median blood concentrations were 2.94 nmol/L (interquartile range (IQR): 1.78-4.98 nmol/L) for cadmium and 0.07 micromol/L (IQR: 0.04-0.09 micromol/L) for lead, i.e., below acute toxicity values. Every doubling of lead concentration was associated with a 1.75 (95% confidence interval (CI): 1.11-2.74) times higher risk for albuminuria. In addition, both cadmium (odds ratio (OR) 1.50 95% CI: 1.02-2.21) and lead (OR 1.83 95% CI: 1.07-3.15) were associated with an increased risk for reduced creatinine clearance. Both passive smoking and active smoking were positively associated with cadmium concentration. Alcohol intake was positively associated with lead concentration. No positive associations were found between dietary intake and cadmium or lead.
Conclusions: The association between cadmium and lead and the prevalence of diabetic kidney disease suggests cadmium and lead might contribute to the development of diabetic kidney disease. Exposure to cadmium and lead could be a so far underappreciated nephrotoxic mechanism of smoking and alcohol consumption.

Gepubliceerd: J Clin Med. 2020;9(8).
Impact factor: 3.303; Q1

3. Applicability and reproducibility of acute myeloid leukaemia stem cell assessment in a multi-centre setting
Hanekamp D, Snel AN, Kelder A, Scholten WJ, Khan N, Metzner M, Irno-Consalvo M, Sugita M, de Jong A, Oude Alink S, Eidhof H, Wilhelm M, Feuring-Buske M, Slomp J, van der Velden VHJ, Sonneveld E, Guzman M, Roboz GJ, Buccisano F, Vyas P, Freeman S, Bachas C, Ossenkoppele GJ, Schuurhuis GJ, Cloos J.

Leukaemic stem cells (LSC) have been experimentally defined as the leukaemia-propagating population and are thought to be the cellular reservoir of relapse in acute myeloid leukaemia (AML). Therefore, LSC measurements are warranted to facilitate accurate risk stratification. Previously, we published the composition of a one-tube flow cytometric assay, characterised by the presence of 13 important membrane markers for LSC detection. Here we present the validation experiments of the assay in several large AML research centres, both in Europe and the United States. Variability within instruments and sample processing showed high correlations between different instruments (Rpearson > 0.91, P < 0.001). Multi-centre testing introduced variation in reported LSC percentages but was found to be below the clinical relevant threshold. Clear gating protocols resulted in all laboratories being able to perform LSC assessment of the validation set. Participating centres were nearly unanimously able to distinguish LSC(high) (>0.03% LSC) from LSC(low) (<0.03% LSC) despite inter-laboratory variation in reported LSC percentages. This study proves that the LSC assay is highly reproducible. These results together with the high prognostic impact of LSC load at diagnosis in AML patients render the one-tube LSC assessment a good marker for future risk classification.

Gepubliceerd: Br J Haematol. 2020;190(6):891-900.
Impact factor: 5.518; Q1

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4. The multiple faces of urinary glucose tetrasaccharide as biomarker for patients with hepatic glycogen storage diseases
Heiner-Fokkema MR, van der Krogt J, de Boer F, Fokkert-Wilts MJ, Maatman R, Hoogeveen IJ, Derks TGJ.

Gepubliceerd: Genet Med. 2020;22(11):1915-6.
Impact factor: 8.904; Q1

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5. Harmonizing light transmission aggregometry in the Netherlands by implementation of the SSC-ISTH guideline
Munnix ICA, Van Oerle R, Verhezen P, Kuijper P, Hackeng CM, Hopman-Kerkhoff HIJ, Hudig F, Van De Kerkhof D, Leyte A, De Maat MPM, Oude Elferink RFM, Ruinemans-Koerts J, Schoorl M, Slomp J, Soons H, Stroobants A, Van Wijk E, Henskens YMC.

Light transmission aggregometry (LTA) is considered the gold standard method for evaluation of platelet function. However, there are a lot of variation in protocols (pre-analytical procedures and agonist concentrations) and results. The aim of our study

was to establish a national LTA protocol, to investigate the effect of standardization and to define national reference values for LTA. The SSC guideline was used as base for a national procedure. Almost all recommendations of the SSC were followed e.g. no adjustment of PRP, citrate concentration of 109 mM, 21 needle gauge, fasting, resting time for whole blood and PRP, centrifugation time, speed and agonists concentrations. LTA of healthy volunteers was measured in a total of 16 hospitals with 5 hospitals before and after standardization. Results of more than 120 healthy volunteers (maximum aggregation %) were collected, with participating laboratories using 4 different analyzers with different reagents. Use of low agonist concentrations showed high variation before and after standardization, with the exception of collagen. For most high agonist concentrations (ADP, collagen, ristocetin, epinephrine and arachidonic acid) variability in healthy subjects decreased after standardization. We can conclude that a standardized Dutch protocol for LTA, based on the SSC guideline, does not result in smaller variability in healthy volunteers for all agonist concentrations.

Gepubliceerd: Platelets. 2020:1-8.
Impact factor: 3.378; Q2

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6. Don't be guided purely by numbers: false increased TSH values due to analytical interference
Tibben NE, Bons JAP, van den Berg SAA, Huisman J, Krabbe JG.

Background: Physicians are often guided by laboratory values. When a clinical presentation does not match laboratory values, one must consider the possibility that these values may be falsely increased or decreased. A common cause is analytical interference.
Case Description: A 57-year-old male, presenting with fatigue and palpitations, had high TSH and normal FT4 values. Although there were no fitting clinical symptoms for these values, the patient was treated with levothyroxine assuming he had subclinical hypothyroidism. TSH levels remained high, however, whereas FT4 levels increased and the patient developed thyrotoxicosis. Eventually, it was discovered that the TSH was falsely elevated.
Conclusion: The patient turned out to have macro TSH, where TSH forms conjunctions with IgG into larger molecules. These conjugates cause a rarely occurring interference during laboratory analysis, resulting in a falsely increased TSH value.

Gepubliceerd: Ned Tijdschr Geneeskd. 2020;164.
Impact factor: nvt; nvt

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7. Aspartame and Phe-Containing Degradation Products in Soft Drinks across Europe
van Vliet K, Melis ES, de Blaauw P, van Dam E, Maatman R, Abeln D, van Spronsen FJ, Heiner-Fokkema MR.

Phenylketonuria and tyrosinemia type 1 are treated with dietary phenylalanine (Phe) restriction. Aspartame is a Phe-containing synthetic sweetener used in many

products, including many 'regular' soft drinks. Its amount is (often) not declared; therefore, patients are advised not to consume aspartame-containing foods. This study aimed to determine the variation in aspartame concentrations and its Phe-containing degradation products in aspartame-containing soft drinks. For this, an LC-MS/MS method was developed for the analysis of aspartame, Phe, aspartylphenylalanine, and diketopiperazine in soft drinks. In total, 111 regularly used soft drinks from 10 European countries were analyzed. The method proved linear and had an inter-assay precision (CV%) below 5% for aspartame and higher CVs% of 4.4-49.6% for the degradation products, as many concentrations were at the limit of quantification. Aspartame and total Phe concentrations in the aspartame-containing soft drinks varied from 103 to 1790 micromol/L (30-527 mg/L) and from 119 to 2013 micromol/L (20-332 mg/L), respectively, and were highly variable among similar soft drinks bought in different countries. Since Phe concentrations between drinks and countries highly vary, we strongly advocate the declaration of the amount of aspartame on soft drink labels, as some drinks may be suitable for consumption by patients with Phe-restricted diets.

Gepubliceerd: Nutrients. 2020;12(6).
Impact factor: 4.546; Q1

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8. Three-year clinical outcome in all-comers with "silent" diabetes, prediabetes, or normoglycemia, treated with contemporary coronary drug-eluting stents: From the BIO-RESORT Silent Diabetes study
Ploumen EH, Buiten RA, Kok MM, Doggen CJM, van Houwelingen KG, Stoel MG, de Man F, Hartmann M, Zocca P, Linssen GCM, Doelman C, Kant GD, von Birgelen C.

Background: Patients with coronary disease may have unknown diabetes or prediabetes. We evaluated 3-year outcomes after percutaneous coronary intervention (PCI) with contemporary drug-eluting stents (DES) in patients with silent diabetes, prediabetes, and normoglycemia.
Methods: All BIO-RESORT trial (NCT01674803) participants without known diabetes, enrolled at our center, were invited for oral glucose tolerance testing (OGTT) and measurements of fasting plasma glucose and glycated hemoglobin (HbA1c).
Results: OGTT detected silent diabetes in 68 (6.9%), prediabetes in 132 (13.4%), and normoglycemia in 788 (79.8%) of all 988 study participants. Follow-up was available in 986 (99.8%) patients. The main endpoint target vessel failure (TVF: cardiac death, target vessel-related myocardial infarction [MI], or target vessel revascularization) differed between groups (14.8, 9.9, and 5.6%; p = .002), driven by MI during the first 48 hr and by cardiac death (p < .001; p = .026). Between 48 hr and 3-years, there was no significant between-group difference in TVF, target vessel MI, and target vessel revascularization. Multivariable analysis demonstrated that silent diabetes was independently associated with TVF (adjusted HR: 2.52, 95%-CI: 1.26-5.03). An alternative diagnostic approach-HbA1c and fasting plasma glucose-detected silent diabetes and prediabetes in 33 (3.3%) and 217 (22.0%) patients, and normoglycemia in 738 (74.7%); TVF rates were 12.1, 7.9, and 6.0% (p = .23).
Conclusion: In patients without known diabetes, abnormal glucose metabolism by OGTT was independently associated with higher 3-year TVF rates after PCI with contemporary DES. This difference was driven by periprocedural MI and cardiac

death. After the first 48 hr, the rates of TVF, target vessel MI, and target vessel revascularization were low and did not differ significantly between metabolic groups.

Gepubliceerd: Catheter Cardiovasc Interv. 2020;96(2):E110-e8.
Impact factor: 2.044; Q3

Totale impact factor: 45.487
Gemiddelde impact factor: 5.686

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

Klinische farmacie

1. Heart failure medication after a first hospital admission and risk of heart failure readmission, focus on beta-blockers and renin-angiotensin-aldosterone system medication: A retrospective cohort study in linked databases
Kruik-Kollöffel WJ, van der Palen J, Doggen CJM, van Maaren MC, Kruik HJ, Heintjes EM, Movig KLL, Linssen GCM.

Background: This study assessed the association between heart failure (HF) medication (angiotensin-converting-enzyme inhibitors (ACEI)/angiotensin-receptor blockers (ARB), beta-blockers (BB), mineralocorticoid-receptor antagonists (MRA) and diuretics) and HF readmissions in a real-world unselected group of patients after a first hospital admission for HF. Furthermore we analysed readmission rates for ACEI versus ARB and for carvedilol versus β1-selective BB and we investigated the effect of HF medication in relation to time since discharge. METHODS AND
Findings: Medication at discharge was determined with dispensing data from the Dutch PHARMO Database Network including 22,476 patients with HF between 2001 and 2015. After adjustment for age, gender, number of medications and year of admission no associations were found for users versus non-users of ACEI/ARB (hazard ratio, HR = 1.01; 95%CI 0.96-1.06), BB (HR = 1.00; 95%CI 0.95-1.05) and readmissions. The risk of readmission for patients prescribed MRA (HR = 1.11; 95%CI 1.05-1.16) or diuretics (HR = 1.17; 95%CI 1.09-1.25) was higher than for non-users. The HR for ARB relative to ACEI was 1.04 (95%CI 0.97-1.12) and for carvedilol relative to β1-selective BB 1.33 (95%CI 1.20-1.46). Post-hoc analyses showed a protective effect shortly after discharge for most medications. For example one month post discharge the HR for ACEI/ARB was 0.77 (95%CI 0.69-0.86). Although we did try to adjust for confounding by indication, probably residual confounding is still present.
Conclusions: Patients who were prescribed carvedilol have a higher or at least a similar risk of HF readmission compared to β1-selective BB. This study showed that all groups of HF medication -some more pronounced than others- were more effective immediately following discharge.

Gepubliceerd: PLoS One. 2020;15(12):e0244231.
Impact factor: 2.740; Q2

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2. Integration of Placental Transfer in a Fetal-Maternal Physiologically Based Pharmacokinetic Model to Characterize Acetaminophen Exposure and Metabolic Clearance in the Fetus
Mian P, Allegaert K, Conings S, Annaert P, Tibboel D, Pfister M, van Calsteren K, van den Anker JN, Dallmann A.

Background and Objective: Although acetaminophen is frequently used during pregnancy, little is known about fetal acetaminophen pharmacokinetics. Acetaminophen safety evaluation has typically focused on hepatotoxicity, while other events (fetal ductal closure/constriction) are also relevant. We aimed to develop a fetal-maternal physiologically based pharmacokinetic (PBPK) model (f-m PBPK) to quantitatively predict placental acetaminophen transfer, characterize fetal

acetaminophen exposure, and quantify the contributions of specific clearance pathways in the term fetus.
Methods: An acetaminophen pregnancy PBPK model was extended with a compartment representing the fetal liver, which included maturation of relevant enzymes. Different approaches to describe placental transfer were evaluated (ex vivo cotyledon perfusion experiments, placental transfer prediction based on Caco-2 cell permeability or physicochemical properties [MoBi(®)]). Predicted maternal and fetal acetaminophen profiles were compared with in vivo observations.
Results: Tested approaches to predict placental transfer showed comparable performance, although the ex vivo approach showed highest prediction accuracy. Acetaminophen exposure in maternal venous blood was similar to fetal venous umbilical cord blood. Prediction of fetal acetaminophen clearance indicated that the median molar dose fraction converted to acetaminophen-sulphate and N-acetyl-p-benzoquinone imine was 0.8% and 0.06%, respectively. The predicted mean acetaminophen concentration in the arterial umbilical cord blood was 3.6 mg/L.
Conclusion: The median dose fraction of acetaminophen converted to its metabolites in the term fetus was predicted. The various placental transfer approaches supported the development of a generic f-m PBPK model incorporating in vivo placental drug transfer. The predicted arterial umbilical cord acetaminophen concentration was far below the suggested postnatal threshold (24.47 mg/L) for ductal closure.

Gepubliceerd: Clin Pharmacokinet. 2020;59(7):911-25.
Impact factor: 4.604; Q1

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3. Physiologically Based Pharmacokinetic Modeling to Characterize Acetaminophen Pharmacokinetics and N-Acetyl-p-Benzoquinone Imine (NAPQI) Formation in Non-Pregnant and Pregnant Women
Mian P, van den Anker JN, van Calsteren K, Annaert P, Tibboel D, Pfister M, Allegaert K, Dallmann A.

Background and Objective: Little is known about acetaminophen (paracetamol) pharmacokinetics during pregnancy. The aim of this study was to develop a physiologically based pharmacokinetic (PBPK) model to predict acetaminophen pharmacokinetics throughout pregnancy.
Methods: PBPK models for acetaminophen and its metabolites were developed in non-pregnant and pregnant women. Physiological and enzymatic changes in pregnant women expected to impact acetaminophen pharmacokinetics were considered. Models were evaluated using goodness-of-fit plots and by comparing predicted pharmacokinetic profiles with in vivo pharmacokinetic data. Predictions were performed to illustrate the average concentration at steady state (C(ss,avg)) values, used as an indicator for efficacy, of acetaminophen achieved following administration of 1000 mg every 6 h. Furthermore, as a measurement of potential hepatotoxicity, the molar dose fraction of acetaminophen converted to N-acetyl-p-benzoquinone imine (NAPQI) was estimated.
Results: PBPK models successfully predicted the pharmacokinetics of acetaminophen and its metabolites in non-pregnant and pregnant women. Predictions resulted in the lowest C(ss,avg) in the third trimester (median [interquartile range]: 4.5 [3.8-5.1] mg/L), while C(ss,avg) was 6.7 [5.9-7.4], 5.6 [4.7-6.3], and 4.9 [4.1-5.5] mg/L

in non-pregnant, first trimester, and second trimester populations, respectively. Assuming a constant raised cytochrome P450 2E1 activity throughout pregnancy, the molar dose fraction of acetaminophen converted to NAPQI was highest during the first trimester (median [interquartile range]: 11.0% [9.1-13.4%]), followed by the second (9.0% [7.5-11.0%]) and third trimester (8.2% [6.8-10.1%]), compared with non-pregnant women (7.7% [6.4-9.4%]).
Conclusion: Acetaminophen exposure is lower in pregnant than in non-pregnant women, and is related to pregnancy duration. Despite these findings, higher dose adjustments cannot be advised yet as it is unknown whether pregnancy affects the toxicodynamics of NAPQI. Information on glutathione abundance during pregnancy and NAPQI in vivo data are required to further refine the presented model.

Gepubliceerd: Clin Pharmacokinet. 2020;59(1):97-110.
Impact factor: 4.604; Q1

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4. Does immediate smart feedback on therapy adherence and inhalation technique improve asthma control in children with uncontrolled asthma? A study protocol of the IMAGINE I study
Sportel ET, Oude Wolcherink MJ, van der Palen J, Lenferink A, Thio BJ, Movig KLL, Brusse-Keizer MGJ.

Background: Many asthmatic children suffer from uncontrolled asthma with frequent exacerbations, despite an optimal treatment plan using inhalation medication. Studies have shown that therapy adherence and inhalation technique are often suboptimal in asthmatic children, but these have traditionally been hard to measure. A novel device functioning as an add-on to the inhaler has been developed to measure both aspects by recording vibration patterns during inhalation. This data can be converted to smart feedback and provided to patients immediately via a mobile application. The aim of this study is to improve asthma control in children between 6 and 18 years old by providing immediate smart feedback on the intake of inhalation medication. Asthma control will be measured by forced expiratory volume in 1 s, (Childhood) Asthma Control Test ((c-)ACT) score, and lung function variability and reversibility.
Methods: The study will be performed in Medisch Spectrum Twente (Enschede, The Netherlands). The goal is to include 68 uncontrolled moderate to severe asthmatic children between 6 and 18 years old who receive controller inhalation medication through the Nexthaler®, Ellipta®, or Spiromax®. The study consists of three phases. Phase 1 is observational and will last 4 weeks to observe the baseline adherence and inhalation technique as monitored by the add-on device. A randomised controlled trial lasting 6 weeks will be performed in phase 2. Patients in the intervention group will receive immediate smart feedback about the performed inhalations via a mobile application. In the control group, adherence and inhalation technique will be monitored, but patients will not receive feedback. In phase 3, also lasting 6 weeks, the feedback will be ceased for all children and revision of current therapy may occur, depending on the findings in phase 2. Asthma control can be assessed by means of spirometry (both at home and in the hospital) and (c-)ACT questionnaires.
Discussion: Immediate smart feedback may improve therapy adherence and inhalation technique, and thus asthma control in children and prevent unnecessary switches to targeted biologics. Performing this study in children is desired, since they are known to react differently to feedback and medication than adults.

Trial registration: Dutch Trial Register NL7705 . Registered on 29 April 2019.

Gepubliceerd: Trials. 2020;21(1):801.
Impact factor: 1.883; Q3

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5. Patients' and providers' perspectives on medication relatedness and potential preventability of hospital readmissions within 30 days of discharge
Uitvlugt EB, Janssen MJA, Siegert CEH, Leenders AJA, van den Bemt BJF, van den Bemt P, Karapinar-Çarkit F.

Background: Hospital readmissions are increasingly used as an indicator of quality in health care. One potential risk factor of readmissions is polypharmacy. No studies have explored the patients' perspectives on the medication relatedness and potential preventability of their readmissions.
Objective: To compare the patients' perspectives on the medication relatedness and potential preventability of their readmissions with the providers' perspectives.
Methods: Patients unplanned readmitted within 30 days after discharge at one of the participating departments of OLVG Hospital in Amsterdam were interviewed during their readmission. Patients' perspectives regarding medication relatedness of their readmissions, the potential preventability, possible preventable interventions, and satisfaction with medication information were examined. Health-care providers also reviewed files of these readmitted patients. Primary outcome was the percentage of medication-related and potentially preventable readmissions according to the patient vs the provider. Descriptive data analysis was used.
Results: According to patients, 36 of 172 (21%) readmissions were medication-related, and of these, 21 (58%) were potentially preventable. According to providers, 26 (15%) readmissions were medication-related and 6 (23%) of these were potentially preventable. Patients and providers agreed on the medication relatedness in 11 of the 172 readmissions, and in two of these, agreement on the potential preventability existed. According to patients, preventive interventions belonged mostly to the hospital level, followed by the primary care level and patient level.
Conclusion: Patients and providers differ substantially on their perspectives regarding the medication relatedness and preventability of readmissions. Patients were more likely to view medication-related readmissions as preventable.

Gepubliceerd: Health Expect. 2020;23(1):212-9.
Impact factor: 3.008; Q2

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6. Improving medication safety in the Intensive Care by identifying relevant drug-drug interactions - Results of a multicenter Delphi study
Bakker T, Klopotowska JE, de Keizer NF, van Marum R, van der Sijs H, de Lange DW, de Jonge E, Abu-Hanna A, Dongelmans DA, SIMPLIFY Study Group, includes Beishuizen A, Movig K, Vermeijden JW

Purpose: Drug-drug interactions (DDIs) may cause adverse outcomes in patients admitted to the Intensive Care Unit (ICU). Computerized decision support systems (CDSSs) may help prevent DDIs by timely showing relevant warning alerts, but knowledge on which DDIs are clinically relevant in the ICU setting is limited.

Therefore, the purpose of this study was to identify DDIs relevant for the ICU.
MATERIALS AND
Methods: We conducted a modified Delphi procedure with a Dutch multidisciplinary expert panel consisting of intensivists and hospital pharmacists to assess the clinical relevance of DDIs for the ICU. The procedure consisted of two rounds, each included a questionnaire followed by a live consensus meeting.
Results: In total the clinical relevance of 148 DDIs was assessed, of which agreement regarding the relevance was reached for 139 DDIs (94%). Of these 139 DDIs, 53 (38%) were considered not clinically relevant for the ICU setting.
Conclusions: A list of clinically relevant DDIs for the ICU setting was established on a national level. The clinical value of CDSSs for medication safety could be improved by focusing on the identified clinically relevant DDIs, thereby avoiding alert fatigue.

Gepubliceerd: J Crit Care. 2020;57:134-40.
Impact factor: 2.685; Q3

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7. 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). 2020;29(1):e13185.
Impact factor: 2.161; Q1

Totale impact factor: 21.685
Gemiddelde impact factor: 3.098

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 13.252
Gemiddelde impact factor: 3.313

Longgeneeskunde

1. Optimization of CT windowing for diagnosing invasiveness of adenocarcinoma presenting as sub-solid nodules
Cui X, Fan S, Heuvelmans MA, Han D, Zhao Y, Groen HJM, Dorrius MD, Oudkerk M, de Bock GH, Vliegenthart R, Ye Z.

Purpose: To evaluate the optimal window setting to diagnose the invasiveness of lung adenocarcinoma in sub-solid nodules (SSNs).
Methods: We retrospectively included 437 SSNs and randomly divided them 3:1 into a training group (327) and a testing group (110). The presence of a solid component was regarded as indicator of invasiveness. At fixed window level (WL) of 35 Hounsfield Units (HU), two readers adjusted the window width (WW) in the training group and recorded once a solid component appeared or disappeared on CT images acquired at 120 kVp. The optimal WW cut-off value to differentiate between invasive and pre-invasive lesions, based on the receiver operating characteristic (ROC) curve, was defined as "core" WW. The diagnostic performances of the mediastinal window setting (WW/WL, 350/35 HU) and core window setting were then compared in the testing group.
Results: Of the 437 SSNs, 88 were pre-invasive [17 atypical adenomatous hyperplasia (AAH) and 71 adenocarcinoma in situ (AIS)], 349 were invasive [233 minimally invasive adenocarcinoma (MIA), 116 invasive adenocarcinoma (IA)]. In training group, the core WW of 1175 HU was the optimal cut-off to detect solid components of SSNs (AUC:0.79). In testing group, the sensitivity, specificity, positive, negative predictive value, and diagnostic accuracy for SSN invasiveness were 49.4%, 90.5%, 95.7%, 29.7%, and 57.3% for mediastinal window setting, and 87.6%, 76.2%, 91.6%, 76.2%, and 85.5% for core window setting.
Conclusion: At 120 kVp, core window setting (WW/WL, 1175/35 HU) outperformed the traditional mediastinal window setting to diagnose the invasiveness of SSNs.

Gepubliceerd: Eur J Radiol. 2020;128:108981.
Impact factor: 2.687; Q2

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2. Clinical characteristics and work-up of small to intermediate-sized pulmonary nodules in a Chinese dedicated cancer hospital
Cui X, Han D, Heuvelmans MA, Du Y, Zhao Y, Zhang L, Groen HJM, de Bock GH, Dorrius MD, Oudkerk M, Vliegenthart R, Ye Z.

Objectives: To evaluate the characteristics and work-up of small to intermediate-sized pulmonary nodules in a Chinese dedicated cancer hospital.
Methods: Patients with pulmonary nodules 4-25 mm in diameter detected via computed tomography (CT) in 2013 were consecutively included. The analysis was restricted to patients with a histological nodule diagnosis or a 2-year follow-up period without nodule growth confirming benign disease. Patient information was collected from hospital records.
Results: Among the 314 nodules examined in 299 patients, 212 (67.5%) nodules in 206 (68.9%) patients were malignant. Compared to benign nodules, malignant nodules were larger (18.0 mm vs. 12.5 mm, $P < 0.001$), more often partly solid

(16.0% vs. 4.7%, P < 0.001) and more often spiculated (72.2% vs. 41.2%, P < 0.001), with higher density in contrast-enhanced CT (67.0 HU vs. 57.5 HU, P = 0.015). Final diagnosis was based on surgery in 232 out of 314 (73.9%) nodules, 166 of which were identified as malignant [30 (18.1%) stage III or IV] and 66 as benign. In 36 nodules (11.5%), diagnosis was confirmed by biopsy and the remainder verified based on stability of nodule size at follow-up imaging (n = 46, 14.6%). Among 65 nodules subjected to gene (EGFR) mutation analyses, 28 (43.1%) cases (EGFR19 n = 13; EGFR21 n = 15) were identified as EGFR mutant and 37 (56.9%) as EGFR wild-type. Prior to surgery, the majority of patients [n = 194 (83.6%)] received a contrast-enhanced CT scan for staging of both malignant [n = 140 (84.3%)] and benign [n = 54 (81.8%)] nodules. Usage of positron emission tomography (PET)-CT was relatively uncommon [n = 38 (16.4%)].
Conclusions: CT-derived nodule assessment assists in diagnosis of small to intermediate- sized malignant pulmonary nodules. Currently, contrast-enhanced CT is commonly used as the sole diagnostic confirmation technique for pre-surgical staging, often resulting in surgery for late-stage disease and unnecessary surgery in cases of benign nodules.

Gepubliceerd: Cancer Biol Med. 2020;17(1):199-207.
Impact factor: 5.432; Q1

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3. A Subsolid Nodules Imaging Reporting System (SSN-IRS) for Classifying 3 Subtypes of Pulmonary Adenocarcinoma
Cui X, Heuvelmans MA, Fan S, Han D, Zheng S, Du Y, Zhao Y, Sidorenkov G, Groen HJM, Dorrius MD, Oudkerk M, de Bock GH, Vliegenthart R, Ye Z.

Objectives: To develop an imaging reporting system for the classification of 3 adenocarcinoma subtypes of computed tomography (CT)-detected subsolid pulmonary nodules (SSNs) in clinical patients.
Methods: Between November 2011 and October 2017, 437 pathologically confirmed SSNs were retrospectively identified. SSNs were randomly divided 2:1 into a training group (291 cases) and a testing group (146 cases). CT-imaging characteristics were analyzed using multinomial univariable and multivariable logistic regression analysis to identify discriminating factors for the 3 adenocarcinoma subtypes (pre-invasive lesions, minimally invasive adenocarcinoma, and invasive adenocarcinoma). These factors were used to develop a classification and regression tree model. Finally, an SSN Imaging Reporting System (SSN-IRS) was constructed based on the optimized classification model. For validation, the classification performance was evaluated in the testing group.
Results: Of the CT-derived characteristics of SSNs, qualitative density (nonsolid or part-solid), core (non-core or core), semantic features (pleural indentation, vacuole sign, vascular invasion), and diameter of solid component (≤6 mm or >6 mm), were the most important factors for the SSN-IRS. The total sensitivity, specificity, and diagnostic accuracy of the SSN-IRS was 89.0% (95% confidence interval [CI], 84.8%-92.4%), 74.6% (95% CI, 70.8%-78.1%), and 79.4% (95% CI, 76.5%-82.0%) in the training group and 84.9% (95% CI, 78.1%-90.3%), 68.5% (95% CI, 62.8%-73.8%), and 74.0% (95% CI, 69.6%-78.0%) in the testing group, respectively.
Conclusions: The SSN-IRS can classify 3 adenocarcinoma subtypes using CT-based characteristics of subsolid pulmonary nodules. This classification tool can help

clinicians to make follow-up recommendations or decisions for surgery in clinical patients with SSNs.

Gepubliceerd: Clin Lung Cancer. 2020;21(4):314-25.e4.
Impact factor: 3.550; Q2

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4. Ventilating two patients with one ventilator: technical setup and laboratory testing
de Jongh FHC, de Vries HJ, Warnaar RSP, Oppersma E, Verdaasdonk R, Heunks LMA, Doorduin J.

With a modified circuit, it is feasible to ventilate two patients with one ventilator over a relevant range of compliances. Adding inspiratory resistance allows individual titration of tidal volume, and incorporating one-way valves prevents pendelluft. https://bit.ly/3ex8SYP.

Gepubliceerd: ERJ Open Res. 2020;6(2):00256-2020.
Impact factor: nvt; nvt

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5. Lung cancer occurrence attributable to passive smoking among never smokers in China: a systematic review and meta-analysis
Du Y, Cui X, Sidorenkov G, Groen HJM, Vliegenthart R, Heuvelmans MA, Liu S, Oudkerk M, de Bock GH.

Background: Quantifying the occurrence of lung cancer due to passive smoking is a necessary step when forming public health policy. In this study, we estimated the proportion of lung cancer cases attributable to passive smoking among never smokers in China.
Methods: Six databases were searched up to July 2019 for original observational studies reporting relative risks (RRs) or odds ratios (ORs) for the occurrence of lung cancer associated with passive smoking in Chinese never smokers. The population attributable fraction (PAF) was then calculated using the combined proportion of lung cancer cases exposed to passive smoking and the pooled ORs from meta-analysis. Data are reported with their 95% confidence intervals.
Results: We identified 31 case-control studies of never smokers and no cohort studies. These comprised 9,614 lung cancer cases and 13,093 controls. The overall percentages of lung cancers attributable to passive smoking among never smokers were 15.5% (9.0-21.4%) for 9 population-based studies and 22.7% (16.6-28.3%) for 22 hospital-based studies. The PAFs for women were 17.9% (11.4-24.0%) for the population-based studies and 20.9% (14.7-26.7%) for the hospital-based studies. The PAF for men was only calculable for hospital-based studies, which was 29.0% (95% CI: 8.0-45.2%). Among women, the percentage of lung cancer cases attributable to household exposure (19.5%) was much higher than that due to workplace exposure (7.2%).
Conclusions: We conclude that approximately 16% of lung cancer cases among never smokers in China are potentially attributable to passive smoking. This is slightly higher among women (around 18%), with most cases occurring due to household exposure.

Gepubliceerd: Transl Lung Cancer Res. 2020;9(2):204-17.
Impact factor: 5.132; Q1

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6. The use of oximetry and a questionnaire in primary care enables exclusion of a subsequent obstructive sleep apnea diagnosis
Fabius TM, Benistant JR, Pleijhuis RG, van der Palen J, Eijsvogel MMM.

Purpose: The study aims to prospectively validate the prognostic value of oximetry alone or combined in a two-step strategy with a questionnaire for the exclusion of obstructive sleep apnea (OSA) in primary care.
Methods: A total of 140 subjects with suspected OSA were included from 54 participating primary care practices. All subjects completed the Philips questionnaire and underwent one night of oximetry prior to referral to a sleep center. The prognostic value of two strategies was evaluated against the diagnosis of the sleep center as the gold standard: (1) assume OSA and subsequently refer to a sleep center if the oxygen desaturation index (ODI) is ≥ 5 and (2) assume OSA and refer to a sleep center if the Philips questionnaire score is ≥ 55% (regardless of the ODI) or if the Philips questionnaire score is < 55% and the ODI is ≥ 5.
Results: OSA was diagnosed in the sleep centers in 100 (71%) of the included subjects. Using ODI ≥ 5 alone resulted in a sensitivity of 99.0%, a specificity of 50.0%, a negative predictive value of 95.2%, and a positive predictive value 83.2%. Using the two-step strategy, oximetry would be performed on 39% of the subjects. This strategy resulted in a sensitivity of 100%, a specificity of 35.0%, a negative predictive value of 100%, and a positive predictive value of 79.4%.
Conclusions: In a Dutch primary care population with a clinical suspicion of OSA and low frequency of cardiovascular comorbidities, the use of oximetry alone or combined in a two-step strategy with a questionnaire enables exclusion of a sleep center diagnosis of OSA.

Gepubliceerd: Sleep Breath. 2020;24(1):151-8.
Impact factor: 2.162; Q3

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7. New Fissure-Attached Nodules in Lung Cancer Screening: A Brief Report From The NELSON Study
Han D, Heuvelmans MA, van der Aalst CM, van Smoorenburg LH, Dorrius MD, Rook M, Nackaerts K, Walter JE, Groen HJM, Vliegenthart R, de Koning HJ, Oudkerk M.

Introduction: In incidence lung cancer screening rounds, new pulmonary nodules are regular findings. They have a higher lung cancer probability than baseline nodules. Previous studies have shown that baseline perifissural nodules (PFNs) represent benign lesions. Whether this is also the case for incident PFNs is unknown. This study evaluated newly detected nodules in the Dutch-Belgian randomized-controlled NELSON study with respect to incidence of fissure-attached nodules, their classification, and lung cancer probability.
Methods: Within the NELSON trial, 7557 participants underwent baseline screening between April 2004 and December 2006. Participants with new nodules detected after baseline were included. Nodules were classified based on location and

attachment. Fissure-attached nodules were re-evaluated to be classified as typical, atypical, or non-PFN by two radiologists without knowledge of participant lung cancer status.
Results: One thousand four hundred eighty-four new nodules were detected in 949 participants (77.4% male, median age 59 years [interquartile range: 55-63 years]) in the second, third, and final NELSON screening round. Based on 2-year follow-up or pathology, 1393 nodules (93.8%) were benign. In total, 97 (6.5%) were fissure-attached, including 10 malignant nodules. None of the new fissure-attached malignant nodules was classified as typical or atypical PFN.
Conclusions: In the NELSON study, 6.5% of incident lung nodules were fissure-attached. None of the lung cancers that originated from a new fissure-attached nodule in the incidence lung cancer screening rounds was classified as a typical or atypical PFN. Our results suggest that also in the case of a new PFN, it is highly unlikely that these PFNs will be diagnosed as lung cancer.

Gepubliceerd: J Thorac Oncol. 2020;15(1):125-9.
Impact factor: 13.357; Q1

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8. Current practice patterns of outpatient management of acute pulmonary embolism: A post-hoc analysis of the YEARS study
Hendriks SV, Bavalia R, van Bemmel T, Bistervels IM, Eijsvogel M, Faber LM, Fogteloo J, Hofstee HMA, van der Hulle T, Iglesias Del Sol A, Kruip M, Mairuhu ATA, Middeldorp S, Nijkeuter M, Huisman MV, Klok FA.

Background: Studies have shown the safety of home treatment of patients with pulmonary embolism (PE) at low risk of adverse events. Management studies focusing on home treatment have suggested that 30% to 55% of acute PE patients could be treated at home, based on the HESTIA criteria, but data from day-to-day clinical practice are largely unavailable. AIM: To determine current practice patterns of home treatment of acute PE in the Netherlands.
Method: We performed a post-hoc analysis of the YEARS study. The main outcomes were the proportion of patients who were discharged <24 h and reasons for admission if treated in hospital. Further, we compared the 3-month incidence of PE-related unscheduled readmissions between patients treated at home and in hospital.
Results: Of the 404 outpatients with PE included in this post-hoc analysis of the YEARS study, 184 (46%) were treated at home. The median duration of admission of the hospitalized patients was 3.0 days. The rate of PE-related readmissions of patients treated at home was 9.7% versus 8.6% for hospitalized patients (crude hazard ratio 1.1 (95% CI 0.57-2.1)). The 3-month incidence of any adverse event was 3.8% in those treated at home (2 recurrent VTE, 3 major bleedings and two deaths) compared to 10% in the hospitalized patients (3 recurrent VTE, 6 major bleedings and fourteen deaths).
Conclusions: In the YEARS study, 46% of patients with PE were treated at home with low incidence of adverse events. PE-related readmission rates were not different between patients treated at home or in hospital.

Gepubliceerd: Thromb Res. 2020;193:60-5.
Impact factor: 2.869; Q2

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9. Reasons for Hospitalization of Patients with Acute Pulmonary Embolism Based on the Hestia Decision Rule
Hendriks SV, den Exter PL, Zondag W, Brouwer R, Eijsvogel M, Grootenboers MJ, Faber LM, Heller-Baan R, Hofstee HMA, Iglesias Del Sol A, Kruip M, Mairuhu ATA, Melissant CF, Peltenburg HG, van de Ree MA, Serné EH, Huisman MV, Klok FA.

Background: The Hestia criteria can be used to select pulmonary embolism (PE) patients for outpatient treatment. The subjective Hestia criterion "medical/social reason for admission" allows the treating physician to consider any patient-specific circumstances in the final management decision. It is unknown how often and why this criterion is scored.
Methods: This is a patient-level post hoc analysis of the combined Hestia and Vesta studies. The main outcomes were the frequency of all scored Hestia items in hospitalized patients and the explicit reason for scoring the subjective criterion. Hemodynamic parameters and computed tomography-assessed right ventricular (RV)/left ventricular (LV) ratio of those only awarded with the subjective criterion were compared with patients treated at home.
Results: From the 1,166 patients screened, data were available for all 600 who were hospitalized. Most were hospitalized to receive oxygen therapy (45%); 227 (38%) were only awarded with the subjective criterion, of whom 51 because of "intermediate to intermediate-high risk PE." Compared with patients with intermediate risk PE (RV/LV ratio > 1.0) treated at home (179/566, 32%), hospitalized patients with only the subjective criterion had a higher mean RV/LV ratio (mean difference +0.30, 95% confidence interval [CI] 0.19-0.41) and a higher heart rate (+18/min, 95% CI 10-25). No relevant differences were observed for other hemodynamic parameters.
Conclusion: The most frequent reason for hospital admission was oxygen therapy. In the decision to award the subjective criterion as sole argument for admission, the severity of the RV overload and resulting hemodynamic response of the patient was taken into account rather than just abnormal RV/LV ratio.

Gepubliceerd: Thromb Haemost. 2020;120(8):1217-20.
Impact factor: 4.385; Q1

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10. Uncertain Value of High-sensitive Troponin T for Selecting Patients With Acute Pulmonary Embolism for Outpatient Treatment by Hestia Criteria
Hendriks SV, Lankeit M, den Exter PL, Zondag W, Brouwer R, Eijsvogel M, Grootenboers MJ, Faber LM, Heller-Baan R, Hofstee HMA, Iglesias Del Sol A, Mairuhu ATA, Melissant CF, Peltenburg HG, van de Ree MA, Serné EH, Konstantinides S, Klok FA, Huisman MV.

Gepubliceerd: Acad Emerg Med. 2020;27(10):1043-6.
Impact factor: 3.064; Q1

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11. Less Is More in Lung Cancer Risk Prediction Models
Heuvelmans MA, Oudkerk M.

Gepubliceerd: JAMA Netw Open. 2020;3(2):e1921492.

Impact factor: 5.032; Q1

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12. Assessing paediatric exercise-induced bronchoconstriction using electromyography
Keijzer PB, van der Kamp MR, Thio BJ, de Jongh FHC, Driessen JMM.

Background: Asthma is one of the most common chronic diseases in childhood, occurring in up to 10% of all children. Exercise-induced bronchoconstriction (EIB) is indicative of uncontrolled asthma and can be assessed using an exercise challenge test (ECT). However, this test requires children to undergo demanding repetitive forced breathing manoeuvres. We aimed to study the electrical activity of the diaphragm using surface electromyography (EMG) as an alternative measure to assess EIB.
Methods: Forty-two children suspected of EIB performed an ECT wearing a portable EMG amplifier. EIB was defined as a fall in FEV 1 of more than 13%. Children performed spirometry before exercise, and at 1, 3 and 6 min after exercise until the nadir FEV1 was attained and after the use of a bronchodilator. EMG measurements were obtained between spirometry measurements.
Results: Twenty out of 42 children were diagnosed with EIB. EMG peak amplitudes measured at the diaphragm increased significantly more in children with EIB; 4.85 muV (1.82-7.84), compared to children without EIB; 0.20 muV (-0.10-0.54), ($p<0.001$) at the lowest FEV 1 post-exercise. Furthermore, the increase in EMG peak amplitude could accurately distinguish between EIB and non-EIB using a cut-off of 1.15 muV (sensitivity 95%, specificity 91%).
Conclusion: EMG measurements of the diaphragm are strongly related to the FEV1 and can accurately identify EIB. EMG measurements are a less invasive, effort-independent measure to assess EIB and could be an alternative when spirometry is not feasible.

Gepubliceerd: ERJ Open Res. 2020;6(2):00298-2019.
Impact factor: nvt; nvt

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13. Improving lung cancer diagnosis by combining exhaled-breath data and clinical parameters
Kort S, Brusse-Keizer M, Gerritsen JW, Schouwink H, Citgez E, de Jongh F, van der Maten J, Samii S, van den Bogart M, van der Palen J.

Introduction: Exhaled-breath analysis of volatile organic compounds could detect lung cancer earlier, possibly leading to improved outcomes. Combining exhaled-breath data with clinical parameters may improve lung cancer diagnosis.
Methods: Based on data from a previous multi-centre study, this article reports additional analyses. 138 subjects with non-small cell lung cancer (NSCLC) and 143 controls without NSCLC breathed into the Aeonose. The diagnostic accuracy, presented as area under the receiver operating characteristic curve (AUC-ROC), of the Aeonose itself was compared with 1) performing a multivariate logistic regression analysis of the distinct clinical parameters obtained, and 2) using this clinical information beforehand in the training process of the artificial neural network (ANN) for the breath analysis.

Results: NSCLC patients (mean±sd age 67.1±9.1 years, 58% male) were compared with controls (62.1±7.0 years, 40.6% male). The AUC-ROC of the classification value of the Aeonose itself was 0.75 (95% CI 0.69-0.81). Adding age, number of pack-years and presence of COPD to this value in a multivariate regression analysis resulted in an improved performance with an AUC-ROC of 0.86 (95% CI 0.81-0.90). Adding these clinical variables beforehand to the ANN for classifying the breath print also led to an improved performance with an AUC-ROC of 0.84 (95% CI 0.79-0.89).
Conclusions: Adding readily available clinical information to the classification value of exhaled-breath analysis with the Aeonose, either post hoc in a multivariate regression analysis or a priori to the ANN, significantly improves the diagnostic accuracy to detect the presence or absence of lung cancer.

Gepubliceerd: ERJ Open Res. 2020;6(1):00221-2019.
Impact factor: nvt; nvt

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14. It is time to further expand research in tailoring self-management of COPD exacerbations!
Lenferink A, van der Palen J, van der Valk P, Burt MG, Frith PA, Brusse-Keizer MGJ, Effing TW.

Gepubliceerd: Eur Respir J. 2020;55(1):1902225.
Impact factor: 12.339; Q1

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15. Identification of recent exacerbations in COPD patients by electronic nose
van Bragt J, Brinkman P, de Vries R, Vijverberg SJH, Weersink EJM, Haarman EG, de Jongh FHC, Kester S, Lucas A, In 't Veen J, Sterk PJ, Bel EHD, Maitland-van der Zee AH.

Molecular profiling of exhaled breath by electronic nose (eNose) might be suitable as a noninvasive tool that can help in monitoring of clinically unstable COPD patients. However, supporting data are still lacking. Therefore, as a first step, this study aimed to determine the accuracy of exhaled breath analysis by eNose to identify COPD patients who recently exacerbated, defined as an exacerbation in the previous 3 months. Data for this exploratory, cross-sectional study were extracted from the multicentre BreathCloud cohort. Patients with a physician-reported diagnosis of COPD (n=364) on maintenance treatment were included in the analysis. Exacerbations were defined as a worsening of respiratory symptoms requiring treatment with oral corticosteroids, antibiotics or both. Data analysis involved eNose signal processing, ambient air correction and statistics based on principal component (PC) analysis followed by linear discriminant analysis (LDA). Before analysis, patients were randomly divided into a training (n=254) and validation (n=110) set. In the training set, LDA based on PCs 1-4 discriminated between patients with a recent exacerbation or no exacerbation with high accuracy (receiver operating characteristic (ROC)-area under the curve (AUC)=0.98, 95% CI 0.97-1.00). This high accuracy was confirmed in the validation set (AUC=0.98, 95% CI 0.94-1.00). Smoking, health status score, use of inhaled corticosteroids or vital capacity did not influence these results. Exhaled breath analysis by eNose can discriminate with high accuracy between COPD patients who experienced an exacerbation within 3 months prior to

measurement and those who did not. This suggests that COPD patients who recently exacerbated have their own exhaled molecular fingerprint that could be valuable for monitoring purposes.

Gepubliceerd: ERJ Open Res. 2020;6(4):00307-2020.
Impact factor: nvt; nvt

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16. WEARCON: wearable home monitoring in children with asthma reveals a strong association with hospital based assessment of asthma control
van der Kamp MR, Klaver EC, Thio BJ, Driessen JMM, de Jongh FHC, Tabak M, van der Palen J, Hermens HJ.

Background: Asthma is one of the most common chronic diseases in childhood. Regular follow-up of physiological parameters in the home setting, in relation to asthma symptoms, can provide complementary quantitative insights into the dynamics of the asthma status. Despite considerable interest in asthma home-monitoring in children, there is a paucity of scientific evidence, especially on multi-parameter monitoring approaches. Therefore, the aim of this study is to investigate whether asthma control can be accurately assessed in the home situation by combining parameters from respiratory physiology sensors.
Methods: Sixty asthmatic and thirty non-asthmatic children were enrolled in the observational WEARCON-study. Asthma control was assessed according to GINA guidelines by the paediatrician. All children were also evaluated during a 2-week home-monitoring period with wearable devices; a physical activity tracker, a handheld spirometer, smart inhalers, and an ambulatory electrocardiography device to monitor heart and respiratory rate. Multiple logistic regression analysis was used to determine which diagnostic measures were associated with asthma control.
Results: 24 of the 27 uncontrolled asthmatic children and 29 of the 32 controlled asthmatic children could be accurately identified with this model. The final model showed that a larger variation in pre-exercise lung function (OR = 1.34 95%-CI 1.07-1.68), an earlier wake-up-time (OR = 1.05 95%-CI 1.01-1.10), more reliever use (OR = 1.11 95%-CI 1.03-1.19) and a longer respiratory rate recovery time (OR = 1.12 95%-CI 1.05-1.20) were significant contributors to the probability of having uncontrolled asthma.
Conclusions: Home-monitoring of physiological parameters correlates with paediatrician assessed asthma control. The constructed multivariate model identifies 88.9% of all uncontrolled asthmatic children, indicating a high potential for monitoring of asthma control. This may allow healthcare professionals to assess asthma control at home.
Trial registration: Netherlands Trail Register, NL6087 . Registered 14 February 2017.

Gepubliceerd: BMC Med Inform Decis Mak. 2020;20(1):192.
Impact factor: 2.317; Q3

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17. Diaphragmatic electromyography in preterm infants: The influence of electrode positioning
van Leuteren RW, Bekhuis RE, de Waal CG, de Jongh FH, van Kaam AH, Hutten GJ.

Objective: To determine the effect of changing electrode positions on vital signs and respiratory effort parameters measured with transcutaneous electromyography of the diaphragm (dEMG) in preterm infants.
Methods: In this observational study, simultaneous dEMG measurements were performed at the standard position and at one alternative electrode position (randomly assigned to lateral, superior, medial, inferior to the standard placement, or dorsal). The activity of the diaphragm was measured for 1 hour at both positions. Main outcome measures were the agreement in heart rate (HR), respiratory rate (RR), and percentage difference in dEMG parameters of respiratory effort (peak and tonic activity, amplitude, area under the curve, and frequency content) between the standard and alternative electrode positions.
Results: Thirty clinically stable preterm infants (gestational age 30.1 +/- 3.0 weeks) with either no or noninvasive respiratory support were included. Agreement in HR was excellent at all positions (ICC > 0.95) while RR agreement showed more diversity (ICC range 0.40-0.86). Mixed modeling of dEMG parameters revealed that medial and inferior placement measured the weakest signals (median 75.5% and 64.5% lower dEMG amplitude). Lateral electrode placement showed the highest similarity to standard positioning (median 23.5% lower amplitude).
Conclusion: Measuring HR showed high similarity at all positions. However, registration of RR and respiratory effort is clearly influenced by the electrode position. Electrodes in the same transversal plane as the diaphragm, and at sufficient distance from each other, provide the best agreement with the standard positioning.

Gepubliceerd: Pediatr Pulmonol. 2020;55(2):354-9.
Impact factor: 2.534; Q2

Totale impact factor: 64.860
Gemiddelde impact factor: 3.815

Aantal artikelen 1e, 2e of laatste auteur: 8
Totale impact factor: 39.127
Gemiddelde impact factor: 4.891

MDL

1. Substantial and sustained improvement of serrated polyp detection after a simple educational intervention: results from a prospective controlled trial
Bleijenberg AGC, van Leerdam ME, Bargeman M, Koornstra JJ, van Herwaarden YJ, Spaander MC, Sanduleanu S, Bastiaansen BAJ, Schoon EJ, van Lelyveld N, Dekker E, JEG IJ.

Objective: Serrated polyps (SPs) are an important cause of postcolonoscopy colorectal cancers (PCCRCs), which is likely the result of suboptimal SP detection during colonoscopy. We assessed the long-term effect of a simple educational intervention focusing on optimising SP detection.
Design: An educational intervention, consisting of two 45 min training sessions (held 3 years apart) on serrated polyp detection, was given to endoscopists from 9 Dutch hospitals. Hundred randomly selected and untrained endoscopists from other hospitals were selected as control group. Our primary outcome measure was the proximal SP detection rate (PSPDR) in trained versus untrained endoscopists who participated in our faecal immunochemical test (FIT)-based population screening programme.
Results: Seventeen trained and 100 untrained endoscopists were included, who performed 11 305 and 51 039 colonoscopies, respectively. At baseline, PSPDR was equal between the groups (9.3% vs 9.3%). After training, the PSPDR of trained endoscopists gradually increased to 15.6% in 2018. This was significantly higher than the PSPDR of untrained endoscopists, which remained stable around 10% (p=0.018). All below-average (ie, PSPDR ≤6%) endoscopists at baseline improved their PSPDR after training session 1, as did 57% of endoscopists with average PSPDR (6%-12%) at baseline. The second training session further improved the PSPDR in 44% of endoscopists with average PSPDR after the first training.
Conclusion: A simple educational intervention was associated with substantial long-term improvement of PSPDR in a prospective controlled trial within FIT-based population screening. Widespread implementation of such interventions might be an easy way to improve SP detection, which may ultimately result in fewer PCCRCs.
Trial registration number: NCT03902899.

Gepubliceerd: Gut. 2020;69(12):2150-8.
Impact factor: 19.819; Q1

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2. Increased Discontinuation Rates of Anti-TNF Therapy in Elderly Inflammatory Bowel Disease Patients
de Jong ME, Smits LJT, van Ruijven B, den Broeder N, Russel M, Römkens TEH, West RL, Jansen JM, Hoentjen F.

Background and Aims: There is paucity of data on safety and efficacy of anti-tumour necrosis factor [TNF] in elderly inflammatory bowel disease [IBD] patients. We aimed to compare the long-term treatment failure rates and safety of a first anti-TNF agent in IBD patients between different age groups [<40 years/40-59 years/≥60 years].

Methods: IBD patients who started a first anti-TNF agent were identified through IBDREAM, a multicentre prospective IBD registry. Competing risk regression was used to study treatment failure, defined as time to drug discontinuation due to adverse events [AEs] or lack of effectiveness, with discontinuation due to remission as a competing risk.
Results: A total of 895 IBD patients were included; 546 started anti-TNF at age <40 [61.0%], 268 at age 40-59 [29.9%], and 81 at age ≥60 [9.1%]. Treatment failure rate was higher in the two older groups (subhazard rate [SHR] age ≥60 1.46, SHR age 40-59 1.21; p = 0.03). The SHR in the elderly [>60] was 1.52 for discontinuation due to AEs and 1.11 for lack of effectiveness. Concomitant thiopurine use was associated with a lower treatment failure rate (SHR 0.78, 95% confidence interval [CI] 0.62-0.98, p = 0.031). Serious adverse event [SAE] rate, as well as serious infection rate, were significantly higher in elderly IBD patients [61.2 versus 16.0 and 12.4 per 1000 patient-years, respectively] whereas the malignancy rate was low in all age groups.
Conclusions: Elderly IBD patients starting a first anti-TNF agent showed higher treatment failure rates, but concomitant thiopurine use at baseline was associated with lower failure rates. Elderly IBD patients demonstrated higher rates of SAEs and serious infections.

Gepubliceerd: J Crohns Colitis. 2020;14(7):888-95.
Impact factor: 8.658; Q1

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3. Clinical Outcomes of Covid-19 in Patients with Inflammatory Bowel Disease: A Nationwide Cohort Study
Derikx L, Lantinga MA, de Jong DJ, van Dop WA, Creemers RH, Römkens TEH, Jansen JM, Mahmmod N, West RL, Tan A, Bodelier AGL, Gorter MHP, Boekema PJ, Halet ERC, Horjus CS, van Dijk MA, Hirdes MMC, Epping Stippel LSM, Jharap B, Lutgens M, Russel MG, Gilissen LPL, Nauta S, van Bodegraven AA, Hoentjen F.

Background and Aims: The COVID-19 risk and disease course in inflammatory bowel disease (IBD) patients remains uncertain. Therefore, we aimed to assess the clinical presentation, disease course and outcomes of COVID-19 in IBD patients. Second, we determined COVID-19 incidences in IBD patients and compared this with the general population.
Methods: We conducted a multicenter, nationwide IBD cohort study in the Netherlands and identified patients with COVID-19. First, we assessed the COVID-19 disease course and outcomes. Second, we compared COVID-19 incidences between our IBD study cohort and the general Dutch population.
Results: We established an IBD cohort of 34,763 patients. COVID-19 was diagnosed in 100/34,763 patients (0.29%). 20/100 patients (20%) had severe COVID-19 defined as admission to the intensive care unit, mechanical ventilation, and/or death. Hospitalization occurred in 59/100 (59.0%) patients and 13/100 (13.0%) died. All patients who deceased had comorbidities and all but one were > 65 years. In line, we identified > 1 comorbidity as an independent risk factor for hospitalization (OR 4.20, 95% CI 1.58-11.17, p = 0.004). Incidences of COVID-19 between the IBD study cohort and the general population were comparable (287.6 (95% CI 236.6-349.7) versus 333.0 (95% CI 329.3-336.7) per 100,000 patients, respectively; p = 0.15).
Conclusions: Of 100 cases with IBD and COVID-19, 20% developed severe COVID-19, 59% was hospitalized and 13% died. A comparable COVID-19 risk was found

between the IBD cohort (100/34,763 = 0.29%) and the general Dutch population. The presence of > 1 comorbidities was an independent risk factor for hospitalization due to COVID-19.

Gepubliceerd: J Crohns Colitis. 2020;15(4):529-39.
Impact factor: 8.658; Q1

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4. Associations of Pathogenic Variants in MLH1, MSH2, and MSH6 With Risk of Colorectal Adenomas and Tumors and With Somatic Mutations in Patients With Lynch Syndrome

Engel C, Ahadova A, Seppälä TT, Aretz S, Bigirwamungu-Bargeman M, Bläker H, Bucksch K, Büttner R, de Vos Tot Nederveen Cappel WT, Endris V, Holinski-Feder E, Holzapfel S, Hüneburg R, Jacobs M, Koornstra JJ, Langers AM, Lepistö A, Morak M, Möslein G, Peltomäki P, Pylvänäinen K, Rahner N, Renkonen-Sinisalo L, Schulmann K, Steinke-Lange V, Stenzinger A, Strassburg CP, van de Meeberg PC, van Kouwen M, van Leerdam M, Vangala DB, Vecht J, Verhulst ML, von Knebel Doeberitz M, Weitz J, Zachariae S, Loeffler M, Mecklin JP, Kloor M, Vasen HF.

Background and Aims: Lynch syndrome is caused by variants in DNA mismatch repair (MMR) genes and associated with an increased risk of colorectal cancer (CRC). In patients with Lynch syndrome, CRCs can develop via different pathways. We studied associations between Lynch syndrome-associated variants in MMR genes and risks of adenoma and CRC and somatic mutations in APC and CTNNB1 in tumors in an international cohort of patients.
Methods: We combined clinical and molecular data from 3 studies. We obtained clinical data from 2747 patients with Lynch syndrome associated with variants in MLH1, MSH2, or MSH6 from Germany, the Netherlands, and Finland who received at least 2 surveillance colonoscopies and were followed for a median time of 7.8 years for development of adenomas or CRC. We performed DNA sequence analyses of 48 colorectal tumors (from 16 patients with mutations in MLH1, 29 patients with mutations in MSH2, and 3 with mutations in MSH6) for somatic mutations in APC and CTNNB1.
Results: Risk of advanced adenoma in 10 years was 17.8% in patients with pathogenic variants in MSH2 vs 7.7% in MLH1 (P < .001). Higher proportions of patients with pathogenic variants in MLH1 or MSH2 developed CRC in 10 years (11.3% and 11.4%) than patients with pathogenic variants in MSH6 (4.7%) (P = .001 and P = .003 for MLH1 and MSH2 vs MSH6, respectively). Somatic mutations in APC were found in 75% of tumors from patients with pathogenic variants in MSH2 vs 11% in MLH1 (P = .015). Somatic mutations in CTNNB1 were found in 50% of tumors from patients with pathogenic variants in MLH1 vs 7% in MSH2 (P = .002). None of the 3 tumors with pathogenic variants in MSH6 had a mutation in CTNNB1, but all had mutations in APC.
Conclusions: In an analysis of clinical and DNA sequence data from patients with Lynch syndrome from 3 countries, we associated pathogenic variants in MMR genes with risk of adenoma and CRC, and somatic mutations in APC and CTNNB1 in colorectal tumors. If these findings are confirmed, surveillance guidelines might be adjusted based on MMR gene variants.

Gepubliceerd: Gastroenterology. 2020;158(5):1326-33.

Impact factor: 17.373; Q1

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5. Diabetic Ketoacidosis, Hypertriglyceridemia and Abdominal Pain due to Acute Pancreatitis Complicated by Non-immune Haemolytic Anaemia
Joustra ML, Raidt JJ, Droog F, Veneman TF.

The triad of diabetic ketoacidosis, acute pancreatitis and hypertriglyceridemia is a rare phenomenon, with mortality rates of up to 80%. A unique characteristic of the described case is the co-occurrence of non-immune haemolytic anaemia (NIHA) with the complex triad. It is suggested that this presentation is secondary to hyperlipidemia which leads to increased fragility of erythrocytes due to destabilization of red cell membranes. Supportive treatment with intravenous insulin and blood transfusions is the cornerstone of treatment. LEARNING POINTS: The enigmatic triangle of diabetic ketoacidosis (DKA), hypertriglyceridemia and acute pancreatitis is a rare phenomenon occurring in only 4% of DKA cases.This triad can be complicated by non-immune haemolytic anaemia secondary to hyperlipidemia, which leads to increased fragility of the erythrocyte due to destabilization of red cell membranes.Supportive treatment with intravenous insulin administration and blood transfusions is the cornerstone of treatment.

Gepubliceerd: Eur J Case Rep Intern Med. 2020;7(12):002085.
Impact factor: nvt; nvt

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6. Impact of nationwide enhanced implementation of best practices in pancreatic cancer care (PACAP-1): a multicenter stepped-wedge cluster randomized controlled trial
Mackay TM, Smits FJ, Latenstein AEJ, Bogte A, Bonsing BA, Bos H, Bosscha K, Brosens LAA, Hol L, Busch ORC, Creemers GJ, Curvers WL, den Dulk M, van Dieren S, van Driel L, Festen S, van Geenen EJM, van der Geest LG, de Groot DJA, de Groot JWB, Haj Mohammad N, Haberkorn BCM, Haver JT, van der Harst E, Hemmink GJM, de Hingh IH, Hoge C, Homs MYV, van Huijgevoort NC, Jacobs M, Kerver ED, Liem MSL, Los M, Lubbinge H, Luelmo SAC, de Meijer VE, Mekenkamp L, Molenaar IQ, van Oijen MGH, Patijn GA, Quispel R, van Rijssen LB, Römkens TEH, van Santvoort HC, Schreinemakers JMJ, Schut H, Seerden T, Stommel MWJ, Ten Tije AJ, Venneman NG, Verdonk RC, Verheij J, van Vilsteren FGI, de Vos-Geelen J, Vulink A, Wientjes C, Wit F, Wessels FJ, Zonderhuis B, van Werkhoven CH, van Hooft JE, van Eijck CHJ, Wilmink JW, van Laarhoven HWM, Besselink MG.

Background: Pancreatic cancer has a very poor prognosis. Best practices for the use of chemotherapy, enzyme replacement therapy, and biliary drainage have been identified but their implementation in daily clinical practice is often suboptimal. We hypothesized that a nationwide program to enhance implementation of these best practices in pancreatic cancer care would improve survival and quality of life. METHODS/
Design: PACAP-1 is a nationwide multicenter stepped-wedge cluster randomized controlled superiority trial. In a per-center stepwise and randomized manner, best practices in pancreatic cancer care regarding the use of (neo)adjuvant and palliative chemotherapy, pancreatic enzyme replacement therapy, and metal biliary stents are

implemented in all 17 Dutch pancreatic centers and their regional referral networks during a 6-week initiation period. Per pancreatic center, one multidisciplinary team functions as reference for the other centers in the network. Key best practices were identified from the literature, 3 years of data from existing nationwide registries within the Dutch Pancreatic Cancer Project (PACAP), and national expert meetings. The best practices follow the Dutch guideline on pancreatic cancer and the current state of the literature, and can be executed within daily clinical practice. The implementation process includes monitoring, return visits, and provider feedback in combination with education and reminders. Patient outcomes and compliance are monitored within the PACAP registries. Primary outcome is 1-year overall survival (for all disease stages). Secondary outcomes include quality of life, 3- and 5-year overall survival, and guideline compliance. An improvement of 10% in 1-year overall survival is considered clinically relevant. A 25-month study duration was chosen, which provides 80% statistical power for a mortality reduction of 10.0% in the 17 pancreatic cancer centers, with a required sample size of 2142 patients, corresponding to a 6.6% mortality reduction and 4769 patients nationwide.
Discussion: The PACAP-1 trial is designed to evaluate whether a nationwide program for enhanced implementation of best practices in pancreatic cancer care can improve 1-year overall survival and quality of life.
Trial registration: ClinicalTrials.gov, NCT03513705. Trial opened for accrual on 22th May 2018.

Gepubliceerd: Trials. 2020;21(1):334.
Impact factor: 1.883; Q3

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7. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial
Schepers NJ, Hallensleben NDL, Besselink MG, Anten MGF, Bollen TL, da Costa DW, van Delft F, van Dijk SM, van Dullemen HM, Dijkgraaf MGW, van Eijck CHJ, Erkelens GW, Erler NS, Fockens P, van Geenen EJM, van Grinsven J, Hollemans RA, van Hooft JE, van der Hulst RWM, Jansen JM, Kubben F, Kuiken SD, Laheij RJF, Quispel R, de Ridder RJJ, Rijk MCM, Romkens TEH, Ruigrok CHM, Schoon EJ, Schwartz MP, Smeets X, Spanier BWM, Tan A, Thijs WJ, Timmer R, Venneman NG, Verdonk RC, Vleggaar FP, van de Vrie W, Witteman BJ, van Santvoort HC, Bakker OJ, Bruno MJ, Dutch Pancreatitis Study G.

Background: It remains unclear whether urgent endoscopic retrograde cholangiopancreatography (ERCP) with biliary sphincterotomy improves the outcome of patients with gallstone pancreatitis without concomitant cholangitis. We did a randomised trial to compare urgent ERCP with sphincterotomy versus conservative treatment in patients with predicted severe acute gallstone pancreatitis.
Methods: In this multicentre, parallel-group, assessor-masked, randomised controlled superiority trial, patients with predicted severe (Acute Physiology and Chronic Health Evaluation II score >/=8, Imrie score >/=3, or C-reactive protein concentration >150 mg/L) gallstone pancreatitis without cholangitis were assessed for eligibility in 26 hospitals in the Netherlands. Patients were randomly assigned (1:1) by a web-based randomisation module with randomly varying block sizes to urgent ERCP with sphincterotomy (within 24 h after hospital presentation) or conservative

treatment. The primary endpoint was a composite of mortality or major complications (new-onset persistent organ failure, cholangitis, bacteraemia, pneumonia, pancreatic necrosis, or pancreatic insufficiency) within 6 months of randomisation. Analysis was by intention to treat. This trial is registered with the ISRCTN registry, ISRCTN97372133.
Findings: Between Feb 28, 2013, and March 1, 2017, 232 patients were randomly assigned to urgent ERCP with sphincterotomy (n=118) or conservative treatment (n=114). One patient from each group was excluded from the final analysis because of cholangitis (urgent ERCP group) and chronic pancreatitis (conservative treatment group) at admission. The primary endpoint occurred in 45 (38%) of 117 patients in the urgent ERCP group and in 50 (44%) of 113 patients in the conservative treatment group (risk ratio [RR] 0.87, 95% CI 0.64-1.18; p=0.37). No relevant differences in the individual components of the primary endpoint were recorded between groups, apart from the occurrence of cholangitis (two [2%] of 117 in the urgent ERCP group vs 11 [10%] of 113 in the conservative treatment group; RR 0.18, 95% CI 0.04-0.78; p=0.010). Adverse events were reported in 87 (74%) of 118 patients in the urgent ERCP group versus 91 (80%) of 114 patients in the conservative treatment group.
Interpretation: In patients with predicted severe gallstone pancreatitis but without cholangitis, urgent ERCP with sphincterotomy did not reduce the composite endpoint of major complications or mortality, compared with conservative treatment. Our findings support a conservative strategy in patients with predicted severe acute gallstone pancreatitis with an ERCP indicated only in patients with cholangitis or persistent cholestasis.
Funding: The Netherlands Organization for Health Research and Development, Fonds NutsOhra, and the Dutch Patient Organization for Pancreatic Diseases.

Gepubliceerd: Lancet. 2020;396(10245):167-76.
Impact factor: 60.390; Q1

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8. European guidelines on chronic mesenteric ischaemia - joint United European Gastroenterology, European Association for Gastroenterology, Endoscopy and Nutrition, European Society of Gastrointestinal and Abdominal Radiology, Netherlands Association of Hepatogastroenterologists, Hellenic Society of Gastroenterology, Cardiovascular and Interventional Radiological Society of Europe, and Dutch Mesenteric Ischemia Study group clinical guidelines on the diagnosis and treatment of patients with chronic mesenteric ischaemia
Terlouw LG, Moelker A, Abrahamsen J, Acosta S, Bakker OJ, Baumgartner I, Boyer L, Corcos O, van Dijk LJ, Duran M, Geelkerken RH, Illuminati G, Jackson RW, Kärkkäinen JM, Kolkman JJ, Lönn L, Mazzei MA, Nuzzo A, Pecoraro F, Raupach J, Verhagen HJ, Zech CJ, van Noord D, Bruno MJ.

Chronic mesenteric ischaemia is a severe and incapacitating disease, causing complaints of post-prandial pain, fear of eating and weight loss. Even though chronic mesenteric ischaemia may progress to acute mesenteric ischaemia, chronic mesenteric ischaemia remains an underappreciated and undertreated disease entity. Probable explanations are the lack of knowledge and awareness among physicians and the lack of a gold standard diagnostic test. The underappreciation of this disease results in diagnostic delays, underdiagnosis and undertreating of patients with chronic

mesenteric ischaemia, potentially resulting in fatal acute mesenteric ischaemia. This guideline provides a comprehensive overview and repository of the current evidence and multidisciplinary expert agreement on pertinent issues regarding diagnosis and treatment, and provides guidance in the multidisciplinary field of chronic mesenteric ischaemia.

Gepubliceerd: United European Gastroenterol J. 2020;8(4):371-95.
Impact factor: 3.549; Q2

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9. The Incidence of Chronic Mesenteric Ischemia in the Well-Defined Region of a Dutch Mesenteric Ischemia Expert Center
Terlouw LG, Verbeten M, van Noord D, Brusse-Keizer M, Beumer RR, Geelkerken RH, Bruno MJ, Kolkman JJ.

Introduction: This study aimed to determine the incidence of chronic mesenteric ischemia (CMI) and to examine the influence of the etiological cause, location, and severity of a mesenteric artery stenosis on the probability of having CMI.
Methods: A prospective database, containing the details of all patients with suspected CMI referred to a renowned CMI expert center, was used. Patients residing within the expert centers' well-defined region, between January 2014 and October 2019, were included. CMI was diagnosed when patients experienced sustained symptom improvement after treatment.
Results: This study included 358 patients, 75 had a ≥50% atherosclerotic stenosis of 1 vessel (CMI 16%), 96 of 2 or 3 vessels (CMI 81%), 81 celiac artery compression (CMI 25%), and 84 no stenosis (CMI 12%). In total, 138 patients were diagnosed with CMI, rendering a mean incidence of 9.2 (95% confidence interval [CI] 6.2-13.7) per 100,000 inhabitants. Atherosclerotic CMI was most common, with a mean incidence of 7.2 (95% CI 4.6-11.3), followed by median arcuate ligament syndrome 1.3 (95% CI 0.5-3.6) and chronic nonocclusive mesenteric ischemia 0.6 (95% CI 0.2-2.6). The incidence of CMI was highest in female patients (female patients 12.0 [95% CI 7.3-19.6] vs male patients 6.5 [95% CI 3.4-12.5]) and increased with age. CMI was more prevalent in the presence of a ≥70% atherosclerotic single-vessel stenosis of the superior mesenteric artery (40.6%) than the celiac artery (5.6%).
Discussion: The incidence of CMI is higher than previously believed and increases with age. Probability of CMI seems highest in suspected CMI patients with multivessel disease or a ≥70% atherosclerotic single-vessel superior mesenteric artery stenosis.

Gepubliceerd: Clin Transl Gastroenterol. 2020;11(8):e00200.
Impact factor: 3.968; Q2

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10. Role of endoscopic ultrasonography in the diagnostic work-up of idiopathic acute pancreatitis (PICUS): study protocol for a nationwide prospective cohort study
Umans DS, Timmerhuis HC, Hallensleben ND, Bouwense SA, Anten MG, Bhalla A, Bijlsma RA, Boermeester MA, Brink MA, Hol L, Bruno MJ, Curvers WL, van Dullemen HM, van Eijck BC, Erkelens GW, Fockens P, van Geenen EJM, Hazen WL, Hoge CV, Inderson A, Kager LM, Kuiken SD, Perk LE, Poley JW, Quispel R, Römkens TE, van

Santvoort HC, Tan AC, Thijssen AY, Venneman NG, Vleggaar FP, Voorburg AM, van Wanrooij RL, Witteman BJ, Verdonk RC, Besselink MG, van Hooft JE.

Introduction: Idiopathic acute pancreatitis (IAP) remains a dilemma for physicians as it is uncertain whether patients with IAP may actually have an occult aetiology. It is unclear to what extent additional diagnostic modalities such as endoscopic ultrasonography (EUS) are warranted after a first episode of IAP in order to uncover this aetiology. Failure to timely determine treatable aetiologies delays appropriate treatment and might subsequently cause recurrence of acute pancreatitis. Therefore, the aim of the Pancreatitis of Idiopathic origin: Clinical added value of endoscopic UltraSonography (PICUS) Study is to determine the value of routine EUS in determining the aetiology of pancreatitis in patients with a first episode of IAP.
Methods and Analysis: PICUS is designed as a multicentre prospective cohort study of 106 patients with a first episode of IAP after complete standard diagnostic work-up, in whom a diagnostic EUS will be performed. Standard diagnostic work-up will include a complete personal and family history, laboratory tests including serum alanine aminotransferase, calcium and triglyceride levels and imaging by transabdominal ultrasound, magnetic resonance imaging or magnetic resonance cholangiopancreaticography after clinical recovery from the acute pancreatitis episode. The primary outcome measure is detection of aetiology by EUS. Secondary outcome measures include pancreatitis recurrence rate, severity of recurrent pancreatitis, readmission, additional interventions, complications, length of hospital stay, quality of life, mortality and costs, during a follow-up period of 12 months.
Ethics and Dissemination: PICUS is conducted according to the Declaration of Helsinki and Guideline for Good Clinical Practice. Five medical ethics review committees assessed PICUS (Medical Ethics Review Committee of Academic Medical Center, University Medical Center Utrecht, Radboud University Medical Center, Erasmus Medical Center and Maastricht University Medical Center). The results will be submitted for publication in an international peer-reviewed journal.
Trial registration number: Netherlands Trial Registry (NL7066). Prospectively registered.

Gepubliceerd: BMJ Open. 2020;10(8):e035504.
Impact factor: 2.496; Q2

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11. Intestinal stenosis in Crohn's disease shows a generalized upregulation of genes involved in collagen metabolism and recognition that could serve as novel anti-fibrotic drug targets
van Haaften WT, Blokzijl T, Hofker HS, Olinga P, Dijkstra G, Bank RA, Boersema M.

Background and Aims: Crohn's disease (CD) can be complicated by intestinal fibrosis. Pharmacological therapies against intestinal fibrosis are not available. The aim of this study was to determine whether pathways involved in collagen metabolism are upregulated in intestinal fibrosis, and to discuss which drugs might be suitable to inhibit excessive extracellular matrix formation targeting these pathways.
Methods: Human fibrotic and non-fibrotic terminal ileum was obtained from patients with CD undergoing ileocecal resection due to stenosis. Genes involved in collagen metabolism were analyzed using a microfluidic low-density TaqMan array. A literature

search was performed to find potential anti-fibrotic drugs that target proteins/enzymes involved in collagen synthesis, its degradation and its recognition.
Results: mRNA expression of collagen type I (COL1A1, 0.76 ± 0.28 versus 37.82 ± 49.85, p = 0.02) and III (COL3A1, 2.01 ± 2.61 versus 68.65 ± 84.07, p = 0.02) was increased in fibrotic CD compared with non-fibrotic CD. mRNA expression of proteins involved in both intra- and extracellular post-translational modification of collagens (prolyl- and lysyl hydroxylases, lysyl oxidases, chaperones), collagen-degrading enzymes (MMPs and cathepsin-K), and collagen receptors were upregulated in the fibrosis-affected part. A literature search on the upregulated genes revealed several potential anti-fibrotic drugs.
Conclusion: Expression of genes involved in collagen metabolism in intestinal fibrosis affected terminal ileum of patients with CD reveals a plethora of drug targets. Inhibition of post-translational modification and altering collagen metabolism might attenuate fibrosis formation in the intestine in CD. Which compound has the highest potential depends on a combination anti-fibrotic efficacy and safety, especially since some of the enzymes play key roles in the physiology of collagen.

Gepubliceerd: Therap Adv Gastroenterol. 2020;13:1756284820952578.
Impact factor: 3.961; Q2

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12. Serological Biomarkers of Tissue Turnover Identify Responders to Anti-TNF Therapy in Crohn's Disease: A Pilot Study
van Haaften WT, Mortensen JH, Dige AK, Grønbæk H, Hvas CL, Bay-Jensen AC, Karsdal MA, Olinga P, Manon-Jensen T, Dijkstra G.

Introduction: Anti-tumor necrosis factor (TNF) therapy is effective in inducing remission in Crohn's disease in 60% of patients. No serological biomarkers are available, which can predict response to anti-TNF. We aimed to investigate serological markers of collagen turnover reflecting tissue inflammation as predictors of response to anti-TNF.
Methods: In 2 retrospective observational cohorts, markers for matrix metalloproteinase-degraded type III and IV collagens (C3M and C4M, respectively) and for formation of type III and IV collagens (PRO-C3 and PRO-C4, respectively) were measured in serum and compared with standard C-reactive protein in patients with active Crohn's disease who started infliximab (IFX, n = 21) or adalimumab (ADA, n = 21). Disease activity was classified by the Harvey-Bradshaw index (active disease ≥5); response was defined as clinical remission.
Results: Seventeen patients (81%) treated with IFX were in remission at week 14; 15 patients (71%) treated with ADA were in remission at week 8. Serum C4M at baseline was increased in nonresponders compared with responders (IFX: 35.0 ± 2.4 vs 23.2 ± 2.6, P = 0.04, ADA: 53.0 ± 3.2 vs 34.1 ± 2.8, P = 0.006). C4M levels at baseline predicted response in both cohorts (IFX: odds ratio 39 [95% confidence interval, 2.4-523.9] P = 0.02, cutoff 35.2 nmol/L; ADA: odds ratio 26 [95% confidence interval, 1.8-332.5], P = 0.01, cutoff 46.9 nmol/L). C-reactive protein was not able to predict response to anti-TNF.
Discussion: Response to anti-TNF therapy within the first 14 weeks of treatment can be predicted based on baseline levels of basement membrane marker C4M. This marker could be used as biomarker for response to anti-TNF and could aid in early therapy decision making. Validation in larger well-defined cohorts is needed.

Gepubliceerd: Clin Transl Gastroenterol. 2020;11(9):e00217.
Impact factor: 3.968; Q2

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13. Volatile organic compounds in breath can serve as a non-invasive diagnostic biomarker for the detection of advanced adenomas and colorectal cancer
van Keulen KE, Jansen ME, Schrauwen RWM, Kolkman JJ, Siersema PD.

Background: Colorectal cancer (CRC) is the third most common cancer diagnosis in the Western world. AIM: To evaluate exhaled volatile organic compounds (VOCs) as a non-invasive biomarker for the detection of CRC and precursor lesions using an electronic nose.
Methods: In this multicentre study adult colonoscopy patients, without inflammatory bowel disease or (previous) malignancy, were invited for breath analysis. Two-thirds of the breath tests were randomly assigned to develop training models which were used to predict the diagnosis of the remaining patients (external validation). In the end, all data were used to develop final-disease models to further improve the discriminatory power of the algorithms.
Results: Five hundred and eleven breath samples were collected. Sixty-four patients were excluded due to an inadequate breath test (n = 51), incomplete colonoscopy (n = 8) or colitis (n = 5). Classification was based on the most advanced lesion found; CRC (n = 70), advanced adenomas (AAs) (n = 117), non-advanced adenoma (n = 117), hyperplastic polyp (n = 15), normal colonoscopy (n = 125). Training models for CRC and AAs had an area under the curve (AUC) of 0.76 and 0.71 and blind validation resulted in an AUC of 0.74 and 0.61 respectively. Final models for CRC and AAs yielded an AUC of 0.84 (sensitivity 95% and specificity 64%) and 0.73 (sensitivity and specificity 79% and 59%) respectively.
Conclusions: This study suggests that exhaled VOCs could potentially serve as a non-invasive biomarker for the detection of CRC and AAs. Future studies including more patients could further improve the discriminatory potential of VOC analysis for the detection of (pre-)malignant colorectal lesions. (https://clinicaltrials.gov Identifier NCT03488537).

Gepubliceerd: Aliment Pharmacol Ther. 2020;51(3):334-46.
Impact factor: 7.515; Q1

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14. The influence of demographic characteristics on constipation symptoms: a detailed overview
Verkuijl SJ, Meinds RJ, Trzpis M, Broens PMA.

Background: Diagnosing constipation remains difficult and its treatment continues to be ineffective. The reason may be that the symptom patterns of constipation differ in different demographic groups. We aimed to determine the pattern of constipation symptoms in different demographic groups and to define the symptoms that best indicate constipation.
Methods: In this cross-sectional study the Groningen Defecation and Fecal Continence questionnaire was completed by a representative sample of the adult

Dutch population (N = 892). We diagnosed constipation according to the Rome IV criteria for constipation.
Results: The Rome criteria were fulfilled by 15.6% of the study group and we found the highest prevalence of constipation in women and young adults (19.7 and 23.5%, respectively). Symptom patterns differed significantly between constipated respondents of various ages, while we did not observe sex-based differences. Finally, we found a range of constipation symptoms, not included in the Rome IV criteria, that showed marked differences in prevalence between constipated and non-constipated individuals, especially failure to defecate ($\Delta = 41.2\%$).
Conclusions: Primarily, we found that certain symptoms of constipation are age-dependent. Moreover, we emphasize that symptoms of constipation not included in the Rome IV criteria, such as daily failure to defecate and an average duration of straining of more than five minutes, are also reliable indicators of constipation. Therefore, we encourage clinicians to adopt a more comprehensive approach to diagnosing constipation.

Gepubliceerd: BMC Gastroenterol. 2020;20(1):168.
Impact factor: 2.489; Q3

Totale impact factor: 144.727
Gemiddelde impact factor: 10.338

Aantal artikelen 1e, 2e of laatste auteur: 5
Totale impact factor: 14.386
Gemiddelde impact factor: 2.877

Medical School

1. Medication burden in epilepsy: Exploring the impact of non-epilepsy concomitant drugs load
Bunschoten JW, van der Palen J, Sander JW, Thijs RD.

Purpose: To determine the burden of non-epilepsy drugs on people with epilepsy, using administrative health care data.
Methods: The Achmea Health Insurance Database (AHID) contains health claims data from 25 % of the Dutch population. From the AHID, we selected all policyholders with coverage for at least one full calendar year between 2006-2009. We included adults with diagnostic codes for epilepsy and randomly selected two frequency-matched controls per case. We labeled drugs dispensed at least twice per calendar year as chronic and excluded antiseizure medications. We estimated and compared the prevalence of chronic medication use, number of chronic medications used, number of prescriptions dispensed, Rx Risk comorbidity index, and drug burden index (DBI) between people with epilepsy and controls.
Results: Non-epilepsy chronic medication use was more frequent in people with epilepsy than controls (67 % versus 59 %, $p < 0.001$). People with epilepsy had an increased DBI (average 0.19 versus 0.10, $p < 0.001$), used more chronic medications (median 2 versus 1, $p < 0.001$) and had more prescriptions dispensed (median 7 versus 3, $p < 0.001$). The DBI and number of unique chronic medications were higher among older (>60 years) than younger (<60 years) subjects in cases and controls. Non-epilepsy chronic medication use was more prevalent in people with epilepsy across all therapeutic drug classes and most comorbidities measured using the Rx Risk score.
Conclusion: Chronic non-epilepsy medication use is more prevalent among people with epilepsy. The medication burden is higher among elderly with epilepsy and could partially explain the lower quality of life of people with epilepsy with comorbidities.

Gepubliceerd: Seizure. 2020;81:104-10.
Impact factor: 2.522; Q3

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2. Critical Error Frequency and the Impact of Training with Inhalers Commonly used for Maintenance Treatment in Chronic Obstructive Pulmonary Disease
Collier DJ, Wielders P, van der Palen J, Heyes L, Midwinter D, Collison K, Preece A, Barnes N, Sharma R.

Introduction: Training in correct inhaler use, ideally in person or by video demonstration, can minimize errors but is rarely provided in clinics. This open-label, low-intervention study evaluated critical error rates with dry-powder inhalers (DPIs), before and after training, in patients with chronic obstructive pulmonary disease.
Methods: Patients prescribed an inhaled corticosteroid (ICS)/long-acting β(2)-agonist (LABA) (ELLIPTA, Turbuhaler, or DISKUS), long-acting muscarinic antagonist (LAMA)/LABA (ELLIPTA or Breezhaler), or LAMA-only DPI (ELLIPTA, HandiHaler, or Breezhaler) were enrolled. Critical errors were assessed before training (Visit 1 [V1]; primary endpoint) and 6 weeks thereafter (Visit 2 [V2]; secondary endpoint). Logistic

regression models were used to calculate odds ratios (ORs) for between-group comparisons.
Results: The intent-to-treat population comprised 450 patients. At V1, fewer patients made ≥1 critical error with ELLIPTA (10%) versus other ICS/LABA DPIs (Turbuhaler: 40%, OR 4.66, P=0.005; DISKUS: 26%, OR 2.48, P=0.114) and other LAMA or LAMA/LABA DPIs (HandiHaler: 34%, OR 3.50, P=0.026; Breezhaler: 33%, OR 3.94, P=0.012). Critical error rates with the primary ICS/LABA DPI were not significantly different between ELLIPTA ICS/LABA (10%) and ICS/LABA plus LAMA groups (12-25%). Critical errors with the primary ICS/LABA DPI occurred less frequently with ELLIPTA ICS/LABA with or without LAMA (11%) versus Turbuhaler ICS/LABA with or without LAMA (39%, OR 3.99, P<0.001) and DISKUS ICS/LABA with or without LAMA (26%, OR 2.18, P=0.069). Simulating single-inhaler versus multiple-inhaler triple therapy, critical error rates were lower with ELLIPTA fluticasone furoate/vilanterol (FF/VI; 10%) versus ELLIPTA FF/VI plus LAMA (22%), considering errors with either DPI (OR 2.50, P=0.108). At V2, critical error rates decreased for all DPIs/groups, reaching zero only for ELLIPTA. Between-group comparisons were similar to V1.
Conclusion: Fewer patients made critical errors with ELLIPTA versus other ICS/LABA, and LAMA or LAMA/LABA DPIs. The effect of "verbal" training highlights its importance for reducing critical errors with common DPIs.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis. 2020;15:1301-13.
Impact factor: 2.772; Q2

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3. The use of oximetry and a questionnaire in primary care enables exclusion of a subsequent obstructive sleep apnea diagnosis
Fabius TM, Benistant JR, Pleijhuis RG, van der Palen J, Eijsvogel MMM.

Purpose: The study aims to prospectively validate the prognostic value of oximetry alone or combined in a two-step strategy with a questionnaire for the exclusion of obstructive sleep apnea (OSA) in primary care.
Methods: A total of 140 subjects with suspected OSA were included from 54 participating primary care practices. All subjects completed the Philips questionnaire and underwent one night of oximetry prior to referral to a sleep center. The prognostic value of two strategies was evaluated against the diagnosis of the sleep center as the gold standard: (1) assume OSA and subsequently refer to a sleep center if the oxygen desaturation index (ODI) is ≥ 5 and (2) assume OSA and refer to a sleep center if the Philips questionnaire score is ≥ 55% (regardless of the ODI) or if the Philips questionnaire score is < 55% and the ODI is ≥ 5.
Results: OSA was diagnosed in the sleep centers in 100 (71%) of the included subjects. Using ODI ≥ 5 alone resulted in a sensitivity of 99.0%, a specificity of 50.0%, a negative predictive value of 95.2%, and a positive predictive value 83.2%. Using the two-step strategy, oximetry would be performed on 39% of the subjects. This strategy resulted in a sensitivity of 100%, a specificity of 35.0%, a negative predictive value of 100%, and a positive predictive value of 79.4%.
Conclusions: In a Dutch primary care population with a clinical suspicion of OSA and low frequency of cardiovascular comorbidities, the use of oximetry alone or combined in a two-step strategy with a questionnaire enables exclusion of a sleep center diagnosis of OSA.

Gepubliceerd: Sleep Breath. 2020;24(1):151-8.
Impact factor: 2.162; Q3

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4. Severe Hallux Valgus Angle Attended With High Incidence of Nonunion in Arthrodesis of the First Metatarsophalangeal Joint: A Follow-Up Study
Füssenich W, Brusse-Keizer MGJ, Somford MP.

The incidence of nonunion after first metatarsophalangeal joint (MTP-1) arthrodesis was found to be high in our clinic. By raising awareness for the problem, making a uniform surgical treatment protocol, banning the commonly used convex-concave reamers, and promoting solely the use of hand instruments to prepare the joint for arthrodesis, we tried to decrease the numbers of nonunion. This prospective cohort study included all patients who underwent MTP-1 fusion between January 2018 and March 2019. Patients were treated according to a standardized protocol, using hand instruments to prepare the joint for fusion. Anthropometric and therapy-related data were collected and compared with an earlier 2015-2016 cohort that was retrospectively assessed. Furthermore, the frequency of nonunion between convex-concave reamers and hand instruments was compared. A total of 53 patients underwent MTP-1 fusion surgery. The incidence of nonunion was 3.8%, significantly lower than the 24.1% in 2015 to 2016 (p = .002). Multivariate regression analysis showed a 7.11 times higher risk of nonunion in 2015 to 2016 compared with 2018 to 2019 (95% confidence interval [CI] 1.55 to 32.55) (p = .012). Furthermore, an increase of 10° in HVA showed a 1.52 risk of occurrence of nonunion (95% CI 1.07 to 2.17) (p = .021). The use of convex/concave reamers was univariately associated with a 3.61 times higher risk of nonunion (95% CI 1.14 to 11.43) (p = .029); however, after correction for preoperative HVA, the preparation method was no longer associated with the occurrence of nonunion (p = .108). Patients suffering from severe hallux valgus had nonunion in 32.1% of cases. Incidence of nonunion after MTP-1 arthrodesis was significantly reduced by raising awareness and by standardizing the treatment protocol. There was no significant difference in nonunion frequency between the methods of joint surface preparation. Severe hallux valgus is prone to nonunion, and more research into this indication for MTP-1 fusion and outcome is needed.

Gepubliceerd: J Foot Ankle Surg. 2020;59(5):993-6.
Impact factor: 1.043; Q4

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5. Eye movement desensitization and reprocessing (EMDR) in patients with a personality disorder
Hafkemeijer L, de Jongh A, van der Palen J, Starrenburg A.

Background: Little is known about the effects of targeting memories of adverse (childhood) events in people with a personality disorder (PD).
Objective: Determining the effectiveness of brief EMDR therapy in individuals with PD.
Method: In a randomized-controlled trial, 97 outpatients with a PD as main diagnosis were allocated to either five (90 minutes) sessions of EMDR therapy (n = 51) or a

waiting list (WL) control condition (n = 46) followed by 3 months of treatment as usual for their PD. Individuals with posttraumatic stress disorder (PTSD) were excluded. Measurements were performed on psychological symptoms, psychological distress, and personality dysfunctioning. Outcomes were compared at baseline, post-treatment, and at 3-month follow up. Data were analysed as intent-to-treat with linear mixed models.
Results: EMDR therapy yielded significant improvements with medium to large effect sizes for the primary outcomes after treatment, i.e. psychological symptoms (EMDR: d =.42; control group: d =.07), psychological distress (EMDR: d =.69; control group: d =.29), and personality functioning (EMDR: d =.41; control group: d = -.10) within groups. At 3-month follow-up, after 3 months of TAU, improvements were maintained. Significant differences were found between both groups regarding all outcome measures in favour of the EMDR group at post-treatment (ds between -.62 and -.65), and at follow-up, after 3 months of TAU (ds between -.45 and -.53).
Conclusions: The results suggest that EMDR therapy can be beneficial in the treatment of patients with PDs. More rigorous outcome research examining long-term effects and using a longer treatment track is warranted.

Gepubliceerd: Eur J Psychotraumatol. 2020;11(1):1838777.
Impact factor: 4.209; Q1

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6. Recovery of strength after reduced pediatric fractures of the forearm, wrist or hand; A prospective study
Hepping AM, Barvelink B, Ploegmakers JJW, van der Palen J, Geertzen JHB, Bulstra SK, Harbers JS, Stevens M.

Introduction: The way strength recovers after reduction of pediatric fractures of the upper extremity has not previously been the specific scope of research. This is remarkable, since strength measurements are often used as an outcome measure in studies on trauma of the upper extremity. The aim of this study was to evaluate how strength recovers after sustainment of fractures of the forearm, wrist or hand treated by closed or open reduction in children and adolescents in the first 6 months after trauma. How much strength is lost at 6 weeks, 3 months and 6 months after trauma, and is this loss significant? Are there differences in the pattern of recovery between children who underwent a different treatment? And finally, which of the following factors are associated with an increase in the ratio between affected grip strength and expected strength: type of fracture, cast immobilization, occurrence of complications, and degree of pain?
Design: Prospective observational study.
Participants: Children and adolescents aged 4-18 years with a reduced fracture of the forearm, wrist or hand.
Methods: Grip strength, key grip and three-jaw chuck grip were measured twice in each hand 6 weeks, 3 months and 6 months after trauma. Details on fracture type and location, treatment received, cast immobilization and complications were obtained. Hand-dominance and pain were verbally confirmed.
Results: Loss of strength was more prominent and prolonged the more invasive the treatment, hence most extensive in the group receiving open reduction with internal fixation (ORIF), intermediate in the group receiving closed reduction with percutaneous pinning (CRIF), and least extensive in the group undergoing closed

reduction without internal fixation (CR). Besides time passed, gender and age were of significant influence on strength, although there was no difference in pattern of recovery over time between children who received a different treatment. In the period of 6 weeks to 3 months after trauma, female gender, type of fracture sustained and occurrence of an unwanted event were associated with an increased ratio between affected and expected grip strength. For the later phase of recovery, between 3 and 6 months, this was only true for the occurrence of an unwanted event.

Gepubliceerd: PLoS One. 2020;15(4):e0230862.
Impact factor: 2.740; Q2

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7. The Mitotic Activity Index in combination with Her2neu: a strong prognosticator in breast cancer
Jobsen JJ, Struikmans H, van der Palen J, Siemerink E.

Purpose: The aim of this study is to evaluate the prognostic value of the Mitotic Activity Index (MAI) in combination with the human epidermal growth factor receptor (Her2) for distant metastases-free survival (DMFS) and disease-specific survival (DSS) in breast cancer and compare it with the immunohistochemically (IHC) profile types.
Methods: Analyses were based on 2.923 breast-conserving breast cancer specimens with known MAI, Her2 status, and hormone receptor status, resulting in 2.678 Her2MAI combinations, MAI ≤ 12/Her2negative, MAI > 12/Her2negative, MAI > 12/Her2positive, and MAI ≤ 12/Her2positive, and 2.560 IHC profile types, luminal A, luminal B, triple negative, and non-luminal Her2positive.
Results: For DMFS, the MAI > 12/Her2negative combination showed a significantly worse outcome in multivariate analyses compared to the MAI ≤ 12/Her2negative combination. None of the IHC profile types showed significantly different outcomes for DMFS and DSS as compared to luminal A. We performed a separate analysis on age and lymph node status. The significance of MAI > 12/Her2negative seems to be limited to women ≤ 55 years for both DMFS and DSS. However, with respect to DSS, this seems to be limited to node negative cases. The IHC profile types for DSS, luminal B showed a significantly worse outcome for women > 55 years compared to that for luminal A, although it showed rather wide confidence interval.
Conclusion: The MAI > 12/Her2negative combination seems to be a strong prognosticator for DMFS and DSS, particularly for women ≤ 55 years. However, none of the IHC profile types seems to be a prognosticator in breast cancer.

Gepubliceerd: Breast Cancer Res Treat. 2020;181(1):13-21.
Impact factor: 3.831; Q2

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8. Improving lung cancer diagnosis by combining exhaled-breath data and clinical parameters
Kort S, Brusse-Keizer M, Gerritsen JW, Schouwink H, Citgez E, de Jongh F, van der Maten J, Samii S, van den Bogart M, van der Palen J.

Introduction: Exhaled-breath analysis of volatile organic compounds could detect lung cancer earlier, possibly leading to improved outcomes. Combining exhaled-breath data with clinical parameters may improve lung cancer diagnosis.
Methods: Based on data from a previous multi-centre study, this article reports additional analyses. 138 subjects with non-small cell lung cancer (NSCLC) and 143 controls without NSCLC breathed into the Aeonose. The diagnostic accuracy, presented as area under the receiver operating characteristic curve (AUC-ROC), of the Aeonose itself was compared with 1) performing a multivariate logistic regression analysis of the distinct clinical parameters obtained, and 2) using this clinical information beforehand in the training process of the artificial neural network (ANN) for the breath analysis.
Results: NSCLC patients (mean±sd age 67.1±9.1 years, 58% male) were compared with controls (62.1±7.0 years, 40.6% male). The AUC-ROC of the classification value of the Aeonose itself was 0.75 (95% CI 0.69-0.81). Adding age, number of pack-years and presence of COPD to this value in a multivariate regression analysis resulted in an improved performance with an AUC-ROC of 0.86 (95% CI 0.81-0.90). Adding these clinical variables beforehand to the ANN for classifying the breath print also led to an improved performance with an AUC-ROC of 0.84 (95% CI 0.79-0.89).
Conclusions: Adding readily available clinical information to the classification value of exhaled-breath analysis with the Aeonose, either post hoc in a multivariate regression analysis or a priori to the ANN, significantly improves the diagnostic accuracy to detect the presence or absence of lung cancer.

Gepubliceerd: ERJ Open Res. 2020;6(1):00221-2019.
Impact factor: nvt; nvt

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9. Heart failure medication after a first hospital admission and risk of heart failure readmission, focus on beta-blockers and renin-angiotensin-aldosterone system medication: A retrospective cohort study in linked databases
Kruik-Kollöffel WJ, van der Palen J, Doggen CJM, van Maaren MC, Kruik HJ, Heintjes EM, Movig KLL, Linssen GCM.

Background: This study assessed the association between heart failure (HF) medication (angiotensin-converting-enzyme inhibitors (ACEI)/angiotensin-receptor blockers (ARB), beta-blockers (BB), mineralocorticoid-receptor antagonists (MRA) and diuretics) and HF readmissions in a real-world unselected group of patients after a first hospital admission for HF. Furthermore we analysed readmission rates for ACEI versus ARB and for carvedilol versus β1-selective BB and we investigated the effect of HF medication in relation to time since discharge.
Methods and Findings: Medication at discharge was determined with dispensing data from the Dutch PHARMO Database Network including 22,476 patients with HF between 2001 and 2015. After adjustment for age, gender, number of medications and year of admission no associations were found for users versus non-users of ACEI/ARB (hazard ratio, HR = 1.01; 95%CI 0.96-1.06), BB (HR = 1.00; 95%CI 0.95-1.05) and readmissions. The risk of readmission for patients prescribed MRA (HR = 1.11; 95%CI 1.05-1.16) or diuretics (HR = 1.17; 95%CI 1.09-1.25) was higher than for non-users. The HR for ARB relative to ACEI was 1.04 (95%CI 0.97-1.12) and for carvedilol relative to β1-selective BB 1.33 (95%CI 1.20-1.46). Post-hoc analyses showed a protective effect shortly after discharge for most medications. For example

one month post discharge the HR for ACEI/ARB was 0.77 (95%CI 0.69-0.86). Although we did try to adjust for confounding by indication, probably residual confounding is still present.
Conclusions: Patients who were prescribed carvedilol have a higher or at least a similar risk of HF readmission compared to β1-selective BB. This study showed that all groups of HF medication -some more pronounced than others- were more effective immediately following discharge.

Gepubliceerd: PLoS One. 2020;15(12):e0244231.
Impact factor: 2.740; Q2

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10. Can Pediatricians Assess Exercise-Induced Bronchoconstriction From Post-exercise Videos?
Lammers N, van Hoesel MHT, Brusse-Keizer MGJ, van der Palen J, Spenkelink-Visser R, Driessen JMM, Thio BJ.

Objective: Exercise-induced bronchoconstriction (EIB) is a highly prevalent morbidity of childhood asthma and defined by a transient narrowing of the airways during or after physical exercise. An exercise challenge test (ECT) is the reference standard for the diagnosis of EIB. Video evaluation of EIB symptoms could be a practical alternative for the assessment of EIB. We studied the ability of pediatricians to assess EIB from post-exercise videos.
Methods: A clinical assessment was performed in 20 asthmatic children (mean age 11.6 years) and EIB was measured with a standardized ECT performed in cold, dry air. EIB was defined as a fall in forced expiratory volume in 1 s (FEV(1)) of ≥10% post-exercise. Children were filmed before and after exercise in frontal position and bare chested. The clinical assessment results and videos were shown to 20 pediatricians (mean experience 14.4 years). Each assessed EIB severity in 5 random children providing 100 assessments, scored on a continuous rating scale (0-10) and in severity classifications (no, mild, moderate, severe) using a scoring list including physical asthma symptoms. Correlations between predicted scores and objective scores were calculated with Spearman's rho and Cohen's Kappa. A generalized linear model was used to assess the relationship between physical symptoms and fall in FEV(1).
Results: Median fall in FEV(1) after exercise was 15.1% (IQR 1.2-65.1). Pediatricians detected EIB with a sensitivity of 78% (95% CI 66-87%) and a specificity of 40% (95% CI 27-55%). The positive predictive value for a pediatricians' diagnosis of EIB was 61% (95% CI 50-72%). The negative predictive value was 60% (95% CI 42-76%). The agreement between predicted EIB severity classifications and the validated classifications based on the ECT's, was fair [Kappa = 0.36 (95% CI 0.23-0.48)]. The correlation between predicted EIB severity scored on a continuous rating scale and fall in FEV(1) after exercise was weak ($r(s) = 0.39$, $p < 0.001$). Independent predictive variables for fall in FEV(1) were wheezing (-11%), supraclavicular retractions (-8.4%) and a prolonged expiratory phase (-8.8%).
Conclusion: The ability of pediatricians to assess EIB from post-exercise videos is fair at best, implicating that standardized ECT's are still vital in the assessment of EIB.

Gepubliceerd: Front Pediatr. 2020;7:561.

11. Alcohol Avoidance Training as a Mobile App for Problem Drinkers: Longitudinal Feasibility Study
Laurens MC, Pieterse ME, Brusse-Keizer M, Salemink E, Ben Allouch S, Bohlmeijer ET, Postel MG.

Background: Alcohol use is associated with an automatic tendency to approach alcohol, and the retraining of this tendency (cognitive bias modification [CBM]) shows therapeutic promise in clinical settings. To improve access to training and to enhance participant engagement, a mobile version of alcohol avoidance training was developed.
Objective: The aims of this pilot study were to assess (1) adherence to a mobile health (mHealth) app; (2) changes in weekly alcohol use from before to after training; and (3) user experience with regard to the mHealth app.
Methods: A self-selected nonclinical sample of 1082 participants, who were experiencing problems associated with alcohol, signed up to use the alcohol avoidance training app Breindebaas for 3 weeks with at least two training sessions per week. In each training session, 100 pictures (50 of alcoholic beverages and 50 of nonalcoholic beverages) were presented consecutively in a random order at the center of a touchscreen. Alcoholic beverages were swiped upward (away from the body), whereas nonalcoholic beverages were swiped downward (toward the body). During approach responses, the picture size increased to mimic an approach movement, and conversely, during avoidance responses, the picture size decreased to mimic avoidance. At baseline, we assessed sociodemographic characteristics, alcohol consumption, alcohol-related problems, use of other substances, self-efficacy, and craving. After 3 weeks, 37.89% (410/1082) of the participants (posttest responders) completed an online questionnaire evaluating adherence, alcohol consumption, and user satisfaction. Three months later, 19.03% (206/1082) of the participants (follow-up responders) filled in a follow-up questionnaire examining adherence and alcohol consumption.
Results: The 410 posttest responders were older, were more commonly female, and had a higher education as compared with posttest dropouts. Among those who completed the study, 79.0% (324/410) were considered adherent as they completed four or more sessions, whereas 58.0% (238/410) performed the advised six or more training sessions. The study identified a significant reduction in alcohol consumption of 7.8 units per week after 3 weeks (95% CI 6.2-9.4, P<.001; n=410) and another reduction of 6.2 units at 3 months for follow-up responders (95% CI 3.7-8.7, P<.001; n=206). Posttest responders provided positive feedback regarding the fast-working, simple, and user-friendly design of the app. Almost half of the posttest responders reported gaining more control over their alcohol use. The repetitious and nonpersonalized nature of the intervention was suggested as a point for improvement.
Conclusions: This is one of the first studies to employ alcohol avoidance training in a mobile app for problem drinkers. Preliminary findings suggest that a mobile CBM app fulfils a need for problem drinkers and may contribute to a reduction in alcohol use. Replicating these findings in a controlled study is warranted.

Gepubliceerd: JMIR Mhealth Uhealth. 2020;8(4):e16217.

Impact factor: 4.313; Q1

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12. It is time to further expand research in tailoring self-management of COPD exacerbations!
Lenferink A, van der Palen J, van der Valk P, Burt MG, Frith PA, Brusse-Keizer MGJ, Effing TW.

Gepubliceerd: Eur Respir J. 2020;55(1):1902225.
Impact factor: 12.339; Q1

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13. High incidence of (ultra)low oesophageal temperatures during cryoballoon pulmonary vein isolation for atrial fibrillation
Molenaar MMD, Hesselink T, Scholten MF, Kraaier K, Bouman DE, Brusse-Keizer M, Stevenhagen YJ, van Dessel P, Ten Haken B, Grandjean JG, van Opstal JM.

Background: Low oesophageal temperatures (OTs) during cryoballoon pulmonary vein isolation (PVI) have been associated with complications. This study assessed the incidence of low OT in clinical practice during cryoballoon PVI and verified possible predictive values for low OT.
Methods: Consecutive patients who underwent PVI using the second-generation cryoballoon were retrospectively included. The distance from the oesophagus to the different pulmonary veins (PVs) (OP distance), body mass index (BMI), sex, age, balloon temperature and application time were studied as potential predictors of low OTs. Computed tomography was performed before the procedure to determine the OP distance. OT was measured using an oesophageal temperature probe. Applications were ended prematurely if the OT reached <16 °C. Low and ultralow OT were defined as OT <20 and <16 °C respectively.
Results: Two hundred and four patients were included. Low OT was observed in 54 patients (26%) and 27 patients (13%) reached ultralow OTs. OP distance was the only predictor of low OTs after multivariate analysis. A cut-off value of 19 mm showed 96.2% sensitivity and 37.8% specificity in predicting low OTs. No clinically relevant relation was found between low OTs and BMI, age, sex, balloon temperature or application duration.
Conclusions: The incidence of low OT was 26% for cryoballoon PVI. OP distance was the only predictor of low OTs. Since an OP distance <19 mm was present in all patients in at least one PV, we recommend routine OT measurement during PVI cryoballoon therapy to prevent oesophagus-related complications.

Gepubliceerd: Neth Heart J. 2020;28(12):662-9.
Impact factor: 1.933; Q3

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14. Shorter RSPV cryoapplications result in less phrenic nerve injury and similar 1-year freedom from atrial fibrillation
Molenaar MMD, Hesselink T, Ter Bekke RMA, Scholten MF, Manusama R, Pison L, Brusse-Keizer M, Kraaier K, Ten Haken B, Grandjean JG, Timmermans CC, van Opstal JM.

Background: In the 123-study, we prospectively assessed, in a randomized fashion, the minimal cryoballoon application time necessary to achieve pulmonary vein (PV) isolation (PVI) in patients with paroxysmal atrial fibrillation (AF) with the aim to reduce complications by shortening the application duration. The first results of this study demonstrated that shortened cryoballoon applications (<2 minutes) resulted in less phrenic nerve injury (PNI) without compromising acute isolation efficacy for the right PVs. We now report the 1-year follow-up results regarding safety and efficacy of shorter cryoballoon applications.
Methods: A total of 222 patients with AF were randomized to two applications of 1 min "short," 2 min "medium," or 3 min "long" duration, 74 per group. Recurrence of AF and PV reconduction at 1-year follow-up were assessed.
Results: The overall 1-year freedom from AF was 79% and did not differ significantly between the short, medium, and long application groups (77%, 74%, and 85% for short, medium, and long application groups, respectively; P = 0.07). In 30 patients, a redo PVI procedure was performed. For all four PVs, there was no significant difference in reconduction between the three groups. Reconduction was most common in the left superior PV (57%). The right superior PV (RSPV) showed significantly less reconduction (17%) compared to the other PVs.
Conclusions: Shortening cryoballoon applications of the RSPV to <2 minutes results in less PNI, while acute success and 1-year freedom from AF are not compromised. Therefore, shorter cryoballoon applications (especially) in the RSPV could be used to reduce PNI.

Gepubliceerd: Pacing Clin Electrophysiol. 2020;43(10):1173-9.
Impact factor: 1.303; Q4

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15. Effect of the dr. Bart application on healthcare use and clinical outcomes in people with osteoarthritis of the knee and/or hip in the Netherlands; a randomized controlled trial
Pelle T, Bevers K, van der Palen J, van den Hoogen FHJ, van den Ende CHM.

Objective: To evaluate the short-term effects of use of the dr. Bart app, compared to usual care, on the number of secondary health care consultations and clinical outcomes in people with knee/hip OA in the Netherlands.
Method: A randomized controlled design involving participants ≥50 years with self-reported knee and/or hip OA recruited from the community. The number of secondary health care consultations (primary outcome) and secondary outcomes were assessed at baseline, 3 and 6 months via online questionnaires. Data were analyzed using longitudinal mixed models, corrected for baseline values. Due to the design of this study, blinding of participants and researchers was not possible.
Results: In total, 427 eligible participants were allocated to either the dr. Bart group (n = 214) or usual care (n = 213). We found no difference between groups in the number of secondary (i.e., orthopaedic surgeon, rheumatologist, or physician assistant) health care consultations (incidence rate ratio (IRR) 1.20 (95% CI: 0.67; 2.19)). We found positive treatment effects of the dr. Bart app on symptoms (2.6 (95% CI: 0.4; 4.9)), pain (3.5 (95% CI: 0.9; 6.0)), and activities of daily living (2.9 (95% CI: 0.2; 5.6)) on a 0-100 scale, higher score indicating less complaints, but not in any other secondary outcome.

Conclusion: The dr. Bart app did not change the number of secondary health care consultations compared to usual care. However, we found small positive effects (not clinically relevant) on pain, symptoms, and activities of daily living in people with knee/hip OA.
Trial registration: Dutch Trial Register (Trial Number NTR6693/NL6505)

Gepubliceerd: Osteoarthritis Cartilage. 2020;28(4):418-27.
Impact factor: 4.793; Q1

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16. Reply to letter to the editor: 'effect of the dr. Bart application on healthcare use and clinical outcomes in people with osteoarthritis of the knee and/or hip in the Netherlands - a randomized controlled trial'
Pelle T, Bevers K, van der Palen J, van den Hoogen FHJ, van den Ende CHM.

Gepubliceerd: Osteoarthritis Cartilage. 2020;28(11):1494-6.
Impact factor: 4.793; Q1

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17. Comparison of physical activity among different subsets of patients with knee or hip osteoarthritis and the general population
Pelle T, Claassen A, Meessen J, Peter WF, Vliet Vlieland TPM, Bevers K, van der Palen J, van den Hoogen FHJ, van den Ende CHM.

To compare the amount of physical activity (PA) among patients with different subsets of knee or hip osteoarthritis (OA) and the general population. Secondary analyses of data of subjects ≥ 50 years from four studies: a study on the effectiveness of an educational program for OA patients in primary care (n = 110), a RCT on the effectiveness of a multidisciplinary self-management program for patients with generalized OA in secondary care (n = 131), a survey among patients who underwent total joint arthroplasty (TJA) for end-stage OA (n = 510), and a survey among the general population in the Netherlands (n = 3374). The Short QUestionnaire to ASssess Health-enhancing physical activity (SQUASH) was used to assess PA in all 4 studies. Differences in PA were analysed by multivariable linear regression analyses, adjusted for age, body mass index and sex. In all groups, at least one-third of total time spent on PA was of at least moderate-intensity. Unadjusted mean duration (hours/week) of at least moderate-intensity PA was 15.3, 12.3, 18.1 and 17.8 for patients in primary, secondary care, post TJA, and the general population, respectively. Adjusted analyses showed that patients post TJA spent 5.6 h [95% CI: 1.5; 9.7] more time on PA of at least moderate-intensity than patients in secondary care. The reported amount of PA of at least moderate-intensity was high in different subsets of OA and the general population. Regarding the amount of PA in patients with different subsets of OA, there was a substantial difference between patients in secondary care and post TJA patients.

Gepubliceerd: Rheumatol Int. 2020;40(3):383-92.
Impact factor: 1.984; Q3

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18. Asthma control and COPD symptom burden in patients using fixed-dose combination inhalers (SPRINT study)
Roche N, Plaza V, Backer V, van der Palen J, Cerveri I, Gonzalez C, Safioti G, Scheepstra I, Patino O, Singh D.

Previous studies have found suboptimal control of symptom burden to be widespread among patients with asthma and chronic obstructive pulmonary disease (COPD). The Phase IV SPRINT study was conducted in 10 countries in Europe to assess asthma disease control and COPD symptom burden in patients treated with a fixed-dose combination (FDC) of inhaled corticosteroids (ICS) and long-acting beta agonists (LABAs). SPRINT included 1101 patients with asthma and 560 with COPD; all were receiving treatment with an FDC of ICS/LABA, delivered via various inhalers. Data were obtained over a 3-month period, during a single routine physician's office visit. Asthma control was defined as Asthma Control Test (ACT) score >19. COPD symptom burden was assessed by COPD Assessment Test (CAT), with a CAT score <10 defining low COPD symptom burden. Among patients using any ICS/LABA FDC, 62% of patients with asthma had achieved disease control (ACT score >19) and 16% of patients with COPD had low symptom burden (CAT score <10).

Gepubliceerd: NPJ Prim Care Respir Med. 2020;30(1):1.
Impact factor: 3.231; Q1

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19. Patients' User Experience of a Blended Face-to-Face and Web-Based Smoking Cessation Treatment: Qualitative Study
Siemer L, Ben Allouch S, Pieterse ME, Brusse-Keizer M, Sanderman R, Postel MG.

Background: Blended web-based and face-to-face (F2F) treatment is a promising electronic health service because the strengths of one mode of delivery should compensate for the weaknesses of the other.
Objective: The aim of this study was to explore this compensation by examining patients' user experience (UX) in a blended smoking cessation treatment (BSCT) in routine care.
Methods: Data on patients' UX were collected through in-depth interviews (n=10) at an outpatient smoking cessation clinic in the Netherlands. A content analysis of the semantic domains was used to analyze patients' UX. To describe the UX, the Hassenzahl UX model was applied, examining 4 of the 5 key elements of UX from a user's perspective: (1) patients' standards and expectations, (2) apparent character (pragmatic and hedonic attributes), (3) usage situation, and (4) consequences (appeal, emotions, and behavior).
Results: BSCT appeared to be a mostly positively experienced service. Patients had a positive-pragmatic standard and neutral-open expectation toward BSCT at the treatment start. The pragmatic attributes of the F2F sessions were mostly perceived as positive, whereas the pragmatic attributes of the web sessions were perceived as both positive and negative. For the hedonic attributes, there seemed to be a difference between the F2F and web sessions. Specifically, the hedonic attributes of the web sessions were experienced as mostly negative, whereas those of the F2F sessions were experienced as mostly positive. For the usage situation, the physical and social contexts were experienced positively, whereas the task and technical contexts were experienced negatively. Nevertheless, the consequential appeal of

BSCT was positive. However, the consequential emotions and behavior varied, ultimately resulting in diverse combinations of consequential appeal, emotions, and behavior (positive, negative, and mixed).
Conclusions: This study provided insights into the UX of a blended treatment, and the results support the expectation that in a blended treatment, the strengths of one mode of delivery may compensate for the weaknesses of the other. However, in this certain setting, this is mainly achieved in only one way: F2F sessions compensated for the weaknesses of the web sessions. As a practical conclusion, this may mean that the web sessions, supported by the strengths of the F2F sessions, offer an interesting approach for further improving the blended treatment. Our theoretical findings reflect the relevance of the aspects of hedonism, such as fun, joy, or happiness in the UX, which were not mentioned in relation to the web sessions and were only scarcely mentioned in relation to the F2F sessions. Future research should further investigate the role of hedonistic aspects in a blended treatment and whether increased enjoyment of a blended treatment could increase treatment adherence and, ultimately, effectiveness.

Gepubliceerd: JMIR Form Res. 2020;4(6):e14550.
Impact factor: nvt; nvt

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20. Adherence to Blended or Face-to-Face Smoking Cessation Treatment and Predictors of Adherence: Randomized Controlled Trial
Siemer L, Brusse-Keizer MGJ, Postel MG, Ben Allouch S, Sanderman R, Pieterse ME.

Background: Blended face-to-face and web-based treatment is a promising way to deliver smoking cessation treatment. Since adherence has been shown to be an indicator of treatment acceptability and a determinant for effectiveness, we explored and compared adherence and predictors of adherence to blended and face-to-face alone smoking cessation treatments with similar content and intensity.
Objective: The objectives of this study were (1) to compare adherence to a blended smoking cessation treatment with adherence to a face-to-face treatment; (2) to compare adherence within the blended treatment to its face-to-face mode and web mode; and (3) to determine baseline predictors of adherence to both treatments as well as (4) the predictors to both modes of the blended treatment.
Methods: We calculated the total duration of treatment exposure for patients (N=292) of a Dutch outpatient smoking cessation clinic who were randomly assigned either to the blended smoking cessation treatment (n=130) or to a face-to-face treatment with identical components (n=162). For both treatments (blended and face-to-face) and for the two modes of delivery within the blended treatment (face-to-face vs web mode), adherence levels (ie, treatment time) were compared and the predictors of adherence were identified within 33 demographic, smoking-related, and health-related patient characteristics.
Results: We found no significant difference in adherence between the blended and the face-to-face treatments. Participants in the blended treatment group spent an average of 246 minutes in treatment (median 106.7% of intended treatment time, IQR 150%-355%) and participants in the face-to-face group spent 238 minutes (median 103.3% of intended treatment time, IQR 150%-330%). Within the blended group, adherence to the face-to-face mode was twice as high as that to the web mode.

Participants in the blended group spent an average of 198 minutes (SD 120) in face-to-face mode (152% of the intended treatment time) and 75 minutes (SD 53) in web mode (75% of the intended treatment time). Higher age was the only characteristic consistently found to uniquely predict higher adherence in both the blended and face-to-face groups. For the face-to-face group, more social support for smoking cessation was also predictive of higher adherence. The variability in adherence explained by these predictors was rather low (blended R(2)=0.049; face-to-face R(2)=0.076). Within the blended group, living without children predicted higher adherence to the face-to-face mode (R(2)=0.034), independent of age. Higher adherence to the web mode of the blended treatment was predicted by a combination of an extrinsic motivation to quit, a less negative attitude toward quitting, and less health complaints (R(2)=0.164).
Conclusions: This study represents one of the first attempts to thoroughly compare adherence and predictors of adherence of a blended smoking cessation treatment to an equivalent face-to-face treatment. Interestingly, although the overall adherence to both treatments appeared to be high, adherence within the blended treatment was much higher for the face-to-face mode than for the web mode. This supports the idea that in blended treatment, one mode of delivery can compensate for the weaknesses of the other. Higher age was found to be a common predictor of adherence to the treatments. The low variance in adherence predicted by the characteristics examined in this study suggests that other variables such as provider-related health system factors and time-varying patient characteristics should be explored in future research.
Trial registration: Netherlands Trial Register NTR5113;

Gepubliceerd: J Med Internet Res. 2020;22(7):e17207.
Impact factor: 5.034; Q1

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21. Does immediate smart feedback on therapy adherence and inhalation technique improve asthma control in children with uncontrolled asthma? A study protocol of the IMAGINE I study
Sportel ET, Oude Wolcherink MJ, van der Palen J, Lenferink A, Thio BJ, Movig KLL, Brusse-Keizer MGJ.

Background: Many asthmatic children suffer from uncontrolled asthma with frequent exacerbations, despite an optimal treatment plan using inhalation medication. Studies have shown that therapy adherence and inhalation technique are often suboptimal in asthmatic children, but these have traditionally been hard to measure. A novel device functioning as an add-on to the inhaler has been developed to measure both aspects by recording vibration patterns during inhalation. This data can be converted to smart feedback and provided to patients immediately via a mobile application. The aim of this study is to improve asthma control in children between 6 and 18 years old by providing immediate smart feedback on the intake of inhalation medication. Asthma control will be measured by forced expiratory volume in 1 s, (Childhood) Asthma Control Test ((c-)ACT) score, and lung function variability and reversibility.
Methods: The study will be performed in Medisch Spectrum Twente (Enschede, The Netherlands). The goal is to include 68 uncontrolled moderate to severe asthmatic children between 6 and 18 years old who receive controller inhalation medication through the Nexthaler®, Ellipta®, or Spiromax®. The study consists of three phases. Phase 1 is observational and will last 4 weeks to observe the baseline adherence and

inhalation technique as monitored by the add-on device. A randomised controlled trial lasting 6 weeks will be performed in phase 2. Patients in the intervention group will receive immediate smart feedback about the performed inhalations via a mobile application. In the control group, adherence and inhalation technique will be monitored, but patients will not receive feedback. In phase 3, also lasting 6 weeks, the feedback will be ceased for all children and revision of current therapy may occur, depending on the findings in phase 2. Asthma control can be assessed by means of spirometry (both at home and in the hospital) and (c-)ACT questionnaires.
Discussion: Immediate smart feedback may improve therapy adherence and inhalation technique, and thus asthma control in children and prevent unnecessary switches to targeted biologics. Performing this study in children is desired, since they are known to react differently to feedback and medication than adults.
Trial registration: Dutch Trial Register NL7705 . Registered on 29 April 2019.

Gepubliceerd: Trials. 2020;21(1):801.
Impact factor: 1.883; Q3

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22. The Incidence of Chronic Mesenteric Ischemia in the Well-Defined Region of a Dutch Mesenteric Ischemia Expert Center
Terlouw LG, Verbeten M, van Noord D, Brusse-Keizer M, Beumer RR, Geelkerken RH, Bruno MJ, Kolkman JJ.

Introduction: This study aimed to determine the incidence of chronic mesenteric ischemia (CMI) and to examine the influence of the etiological cause, location, and severity of a mesenteric artery stenosis on the probability of having CMI.
Methods: A prospective database, containing the details of all patients with suspected CMI referred to a renowned CMI expert center, was used. Patients residing within the expert centers' well-defined region, between January 2014 and October 2019, were included. CMI was diagnosed when patients experienced sustained symptom improvement after treatment.
Results: This study included 358 patients, 75 had a ≥50% atherosclerotic stenosis of 1 vessel (CMI 16%), 96 of 2 or 3 vessels (CMI 81%), 81 celiac artery compression (CMI 25%), and 84 no stenosis (CMI 12%). In total, 138 patients were diagnosed with CMI, rendering a mean incidence of 9.2 (95% confidence interval [CI] 6.2-13.7) per 100,000 inhabitants. Atherosclerotic CMI was most common, with a mean incidence of 7.2 (95% CI 4.6-11.3), followed by median arcuate ligament syndrome 1.3 (95% CI 0.5-3.6) and chronic nonocclusive mesenteric ischemia 0.6 (95% CI 0.2-2.6). The incidence of CMI was highest in female patients (female patients 12.0 [95% CI 7.3-19.6] vs male patients 6.5 [95% CI 3.4-12.5]) and increased with age. CMI was more prevalent in the presence of a ≥70% atherosclerotic single-vessel stenosis of the superior mesenteric artery (40.6%) than the celiac artery (5.6%).
Discussion: The incidence of CMI is higher than previously believed and increases with age. Probability of CMI seems highest in suspected CMI patients with multivessel disease or a ≥70% atherosclerotic single-vessel superior mesenteric artery stenosis.

Gepubliceerd: Clin Transl Gastroenterol. 2020;11(8):e00200.
Impact factor: 3.968; Q2

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23. Influence of Dietary Advice Including Green Vegetables, Beef, and Whole Dairy Products on Recurrent Upper Respiratory Tract Infections in Children: A Randomized Controlled Trial
van der Gaag E, Brandsema R, Nobbenhuis R, van der Palen J, Hummel T.

Background: Since no treatment exists for children suffering from upper respiratory tract infections (URTIs) without immunological disorders, we searched for a possible tool to improve the health of these children. AIM: We evaluated whether dietary advice (based on food matrix and food synergy), including standard supportive care, can decrease the number and duration of URTIs in children with recurrent URTIs.
Design and Setting: This study was a multicenter randomized controlled trial in two pediatric outpatient clinics in the Netherlands, with 118 children aged one to four years with recurrent URTIs. The dietary advice group received dietary advice plus standard supportive care, while the control group received standard supportive care alone for six months. The dietary advice consisted of green vegetables five times per week, beef three times per week, 300 mL whole milk per day, and whole dairy butter on bread every day. Portion sizes were age-appropriate.
Results and Conclusion: Children in the dietary advice group had 4.8 (1.6-9.5) days per month with symptoms of an URTI in the last three months of the study, compared to 7.7 (4.0-12.3) in the control group ($p = 0.028$). The total number of URTIs during the six-month study period was 5.7 (0.55) versus 6.8 (0.49), respectively ($p = 0.068$). The use of antibiotics was significantly reduced in the dietary advice group, as well as visits to a general practitioner, thereby possibly reducing healthcare costs. The results show a reduced number of days with symptoms of a URTI following dietary advice. The number of infections was not significantly reduced.

Gepubliceerd: Nutrients. 2020;12(1).
Impact factor: 4.546; Q1

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24. A Lifestyle (Dietary) Intervention Reduces Tiredness in Children with Subclinical Hypothyroidism, a Randomized Controlled Trial
van der Gaag E, van der Palen J, Schaap P, van Voorthuizen M, Hummel T.

Background: Subclinical hypothyroidism (SH) in children and adults is a subject for discussion in terms of whether to treat it or not with respect to the short-term clinical implications and consequences of SH and in the long term. If treatment with thyroxine supplementation is not indicated, no other treatment is available. We investigated whether a lifestyle (dietary) intervention improves or normalizes SH or decreases the presence of Thyroid Stimulating Hormone (TSH) and/or tiredness.
Methods: We randomized children aged 1-12 years with SH to the control group (standard care = no treatment) or intervention group (dietary intervention). The dietary intervention consisted of green vegetables, beef, whole milk and butter for 6 months. The rest of the diet remained unchanged. We measured TSH, FreeT4, Lipid profile, Body Mass Index (BMI) and Pediatric Quality of Life (PedQL) multidimensional fatigue scale scores.
Results: In total, 62 children were included. After 6 months, TSH decreased in both groups without a significant difference between the groups ($p = 0.98$). PedQL fatigue scores for sleep ($p = 0.032$) and total fatigue scores ($p = 0.039$) improved significantly

in the intervention group, compared to the control group. No unfavorable effects occurred in the lipid profile or BMI.
Conclusion: The lifestyle (dietary) intervention did not normalize SH and TSH levels, but it significantly reduced tiredness. These results suggest that children's well-being can be improved without medication.

Gepubliceerd: Int J Environ Res Public Health. 2020;17(10).
Impact factor: 2.468; Q2

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25. WEARCON: wearable home monitoring in children with asthma reveals a strong association with hospital based assessment of asthma control
van der Kamp MR, Klaver EC, Thio BJ, Driessen JMM, de Jongh FHC, Tabak M, van der Palen J, Hermens HJ.

Background: Asthma is one of the most common chronic diseases in childhood. Regular follow-up of physiological parameters in the home setting, in relation to asthma symptoms, can provide complementary quantitative insights into the dynamics of the asthma status. Despite considerable interest in asthma home-monitoring in children, there is a paucity of scientific evidence, especially on multi-parameter monitoring approaches. Therefore, the aim of this study is to investigate whether asthma control can be accurately assessed in the home situation by combining parameters from respiratory physiology sensors.
Methods: Sixty asthmatic and thirty non-asthmatic children were enrolled in the observational WEARCON-study. Asthma control was assessed according to GINA guidelines by the paediatrician. All children were also evaluated during a 2-week home-monitoring period with wearable devices; a physical activity tracker, a handheld spirometer, smart inhalers, and an ambulatory electrocardiography device to monitor heart and respiratory rate. Multiple logistic regression analysis was used to determine which diagnostic measures were associated with asthma control.
Results: 24 of the 27 uncontrolled asthmatic children and 29 of the 32 controlled asthmatic children could be accurately identified with this model. The final model showed that a larger variation in pre-exercise lung function (OR = 1.34 95%-CI 1.07-1.68), an earlier wake-up-time (OR = 1.05 95%-CI 1.01-1.10), more reliever use (OR = 1.11 95%-CI 1.03-1.19) and a longer respiratory rate recovery time (OR = 1.12 95%-CI 1.05-1.20) were significant contributors to the probability of having uncontrolled asthma.
Conclusions: Home-monitoring of physiological parameters correlates with paediatrician assessed asthma control. The constructed multivariate model identifies 88.9% of all uncontrolled asthmatic children, indicating a high potential for monitoring of asthma control. This may allow healthcare professionals to assess asthma control at home.
Trial registration: Netherlands Trail Register, NL6087 . Registered 14 February 2017.

Gepubliceerd: BMC Med Inform Decis Mak. 2020;20(1):192.
Impact factor: 2.317; Q3

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26. 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. 2020;24(4):577-88.
Impact factor: 1.368; Q3

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27. The additional value of an algorithm for atrial fibrillation at the stroke unit
van der Maten G, Plas GJJ, Meijs MFL, Brouwers P, Brusse-Keizer MGJ, den Hertog HM.

Background and Purpose: The rate of newly detected (paroxysmal) atrial fibrillation (AF) during inpatient cardiac telemetry is low. The objective of this study was to evaluate the additional diagnostic yield of an automated detection algorithm for AF on telemetric monitoring compared with routine detection by a stroke unit team in patients with recent ischemic stroke or TIA.
Methods: Patients admitted to the stroke unit of Medisch Spectrum Twente with acute ischemic stroke or TIA and no history of AF were prospectively included. All patients had telemetry monitoring, routinely assessed by the stroke unit team. The ST segment and arrhythmia monitoring (ST/AR) algorithm was active, with deactivated AF alarms. After 24 h the detections were analyzed and compared with routine evaluation.
Results: Five hundred and seven patients were included (52.5% male, mean age 70.2 ± 12.9 years). Median monitor duration was 24 (interquartile range 22-27) h. In 6 patients (1.2%) routine analysis by the stroke unit team concluded AF. In 24 patients (4.7%), the ST/AR Algorithm suggested AF. Interrater reliability was low (κ, 0.388, $p < 0.001$). Suggested AF by the algorithm turned out to be false positive in 11 patients. In 13 patients (2.6%) AF was correctly diagnosed by the algorithm. None of the cases detected by routine analysis were missed by the algorithm.
Conclusions: Automated AF detection during 24-h telemetry in ischemic stroke patients is of additional value to detect paroxysmal AF compared with routine analysis by the stroke unit team alone. Automated detections need to be carefully evaluated.

Gepubliceerd: J Stroke Cerebrovasc Dis. 2020;29(8):104930.
Impact factor: 1.787; Q4

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28. DuoResp(®) Spiromax(®) adherence, satisfaction and ease of use: findings from a multi-country observational study in patients with asthma and COPD in Europe (SPRINT)
van der Palen J, Cerveri I, Roche N, Singh D, Plaza V, Gonzalez C, Patino O, Scheepstra I, Safioti G, Backer V.

Objective: Adherence and inhaler technique are often suboptimal in asthma and chronic obstructive pulmonary disease (COPD). New inhalers have been developed to improve these determinants of treatment effectiveness. We assessed treatment adherence, satisfaction, and ease of use of DuoResp(®) Spiromax(®) among SPRINT study participants.
Methods: The Phase IV SPRINT study was conducted in 10 European countries. Asthma and COPD patients were receiving a fixed-dose combination of inhaled corticosteroid (ICS) and long-acting β(2)-agonist (LABA), delivered via various inhalers including DuoResp Spiromax. DuoResp Spiromax users self-assessed adherence using the 8-item Morisky Medication Adherence Scale (MMAS-8(®)), and ease of use and satisfaction using 10-point scales, during a single physician's office visit.
Results: Of 1661 (asthma: n = 1101; COPD: n = 560) SPRINT study participants, 342 (asthma: n = 235; COPD: n = 107) received DuoResp Spiromax prior to inclusion. Overall, 72.5% of DuoResp Spiromax users reported medium or high adherence (MMAS-8 score ≥6). Mean (standard deviation [SD]) satisfaction score for DuoResp Spiromax was 8.9 (1.6). Almost all (98.8%) DuoResp Spiromax users were at least satisfied with their inhaler; 85.4% were very satisfied. Mean (SD) ease of use score for DuoResp Spiromax was 9.1 (1.3).
Conclusions: Asthma and COPD patients using DuoResp Spiromax reported moderate-to-high medication adherence, were very satisfied with their inhaler and found it easy to use.

Gepubliceerd: J Asthma. 2020;57(10):1110-8.
Impact factor: 1.899; Q3

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29. 1-Year Clinical Outcomes of All Comers Treated With 2 Bioresorbable Polymer-Coated Sirolimus-Eluting Stents: Propensity Score-Matched Comparison of the COMBO and Ultrathin-Strut Orsiro Stents
Chandrasekhar J, Kok MM, Kalkman DN, Aquino MB, Zocca P, Woudstra P, Beijk MA, Kerkmeijer LS, Sartori S, Baber U, Tijssen JG, Koch KT, Dangas GD, Colombo A, Pocock S, von Birgelen C, Mehran R, de Winter RJ, COMBO Collaborators and BIO-RESORT Investigators, includes van der Heijden LC, van Houwelingen KG, Stoel MG, de Man FHAF, Louwerenburg JHW, Hartmann M, Zocca P, van der Palen J, Löwik MM.

Objectives: The aim of this study was to determine 1-year safety and efficacy after treatment with the COMBO and Orsiro stents.

Background: The COMBO stainless-steel stent has an anti-CD34(+) antibody coating to capture endothelial progenitor cells, thereby promoting faster endothelialization. The Orsiro is an ultrathin-strut cobalt-chromium stent, covered by an extremely thin layer of amorphous silicon carbide to minimize ion leakage. Both devices elute sirolimus from biodegradable polymers.
Methods: For this analysis we included European patients from the COMBO collaboration, a patient-level pooling of 2 prospective all-comers registries of COMBO stent implantation (n = 2,775), and all patients randomized to the Orsiro stent (n = 1,169) from the Dutch BIO-RESORT (Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population) randomized trial. The main outcome of interest was 1-year target lesion failure, a composite of cardiac death, target vessel myocardial infarction, and clinically driven target lesion revascularization evaluated using propensity score-matched analysis.
Results: At baseline, COMBO patients were older and had more insulin-treated diabetes, renal insufficiency, and other comorbidities. However, Orsiro patients included more current smokers and more acute coronary syndrome presentations. Orsiro patients also received longer stents and had more complex target lesions. After propensity score-matched analysis (n = 862/arm), 1-year target lesion failure occurred in 4.1% of COMBO-treated and 2.7% of Orsiro-treated patients (hazard ratio: 1.55; 95% confidence interval: 0.92 to 2.62; p = 0.10). Definite stent thrombosis occurred in 0.5% of COMBO-treated and 0.5% of Orsiro-treated patients (p = 0.99).
Conclusions: A propensity score-matched comparison of all comers treated with the COMBO or Orsiro stent showed no statistically significant differences. Stent thrombosis risk was low and similar between the stents. (Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population [BIO-RESORT], NCT01674803; MASCOT-Post Marketing Registry [MASCOT], NCT02183454; Prospective Registry to Assess the Long-term Safety and Performance of the Combo Stent [REMEDEE Reg], NCT01874002).

Gepubliceerd: JACC Cardiovasc Interv. 2020;13(7):820-30.
Impact factor: 8.432; Q1

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Totale impact factor: 31.296
Gemiddelde impact factor: 3.130

Neurocentrum

1. EEG reactivity testing for prediction of good outcome in patients after cardiac arrest
Admiraal MM, Horn J, Hofmeijer J, Hoedemaekers CWE, van Kaam CR, Keijzer HM, van Putten M, Schultz MJ, van Rootselaar AF.

Objective: To determine the additional value of EEG reactivity (EEG-R) testing to EEG background pattern for prediction of good outcome in adult patients after cardiac arrest (CA).
Methods: In this post hoc analysis of a prospective cohort study, EEG-R was tested twice a day, using a strict protocol. Good outcome was defined as a Cerebral Performance Category score of 1-2 within 6 months. The additional value of EEG-R per EEG background pattern was evaluated using the diagnostic odds ratio (DOR). Prognostic value (sensitivity and specificity) of EEG-R was investigated in relation to time after CA, sedative medication, different stimuli, and repeated testing.
Results: Between 12 and 24 hours after CA, data of 108 patients were available. Patients with a continuous (n = 64) or discontinuous (n = 19) normal voltage background pattern with reactivity were 3 and 8 times more likely to have a good outcome than without reactivity (continuous: DOR, 3.4; 95% confidence interval [CI], 0.97-12.0; p = 0.06; discontinuous: DOR, 8.0; 95% CI, 1.0-63.97; p = 0.0499). EEG-R was not observed in other background patterns within 24 hours after CA. In 119 patients with a normal voltage EEG background pattern, continuous or discontinuous, any time after CA, prognostic value was highest in sedated patients (sensitivity 81.3%, specificity 59.5%), irrespective of time after CA. EEG-R induced by handclapping and sternal rubbing, especially when combined, had highest prognostic value. Repeated EEG-R testing increased prognostic value.
Conclusion: EEG-R has additional value for prediction of good outcome in patients with discontinuous normal voltage EEG background pattern and possibly with continuous normal voltage. The best stimuli were clapping and sternal rubbing.

Gepubliceerd: Neurology. 2020;95(6):e653-e61.
Impact factor: 8.770; Q1

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2. Absence epilepsy: Characteristics, pathophysiology, attention impairments, and the related risk of accidents. A narrative review
Barone V, van Putten M, Visser GH.

Objective: Absence epilepsy (AE) is related to both cognitive and physical impairments. In this narrative review, we critically discuss the pathophysiology of AE and the impairment of attention in children and adolescents with AE. In particular, we contextualize the attentive dysfunctions of AE with the associated risks, such as accidental injuries.
Data Source: An extensive literature search on attention deficits and the rate of accidental injuries in AE was run. The search was conducted on Scopus, Pubmed, and the online libraries of the University of Twente and Maastricht University. Relevant references of the included articles were added. Retrospective and prospective studies, case reports, meta-analysis, and narrative reviews were

included. Only studies written in English were considered. Date of last search is February 2020. The keywords used were "absence epilepsy" AND "attention"/"awareness", "absence epilepsy" AND "accidental injuries"/"accident*"/"injuries".
Results: Ten retrospective and two prospective studies on cognition and AE were fully screened. Seventeen papers explicitly referring to attention in AE were reviewed. Just one paper was found to specifically focus on accidental injuries and AE, while twelve studies generally referring to epilepsy syndromes - among which AE - and related accidents were included.
Conclusion: Absence epilepsy and attention deficits show some patterns of pathophysiological association. This relation may account for dysfunctions in everyday activities in the pediatric population. Particular metrics, such as the risk related to biking in children with AE, should be used in future studies to address the problem in a novel way and to impact clinical indications.

Gepubliceerd: Epilepsy Behav. 2020;112:107342.
Impact factor: 2.508; Q2

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3. Neurosurgical and Perioperative Management of Chronic Subdural Hematoma
Blaauw J, Jacobs B, den Hertog HM, van der Gaag NA, Jellema K, Dammers R, Lingsma HF, van der Naalt J, Kho KH, Groen RJM.

Objective: Surgery and specifically burr hole craniostomy is the most common first choice treatment of patients with Chronic Subdural Hematoma (CSDH). However, several aspects of neurosurgical and peri-operative management are still a subject of research, such as how to treat bilateral CSDH and the anesthetic approach. We aim to investigate the effect of the surgical approach to bilateral CSDH and the effect of anesthesia modality on outcome of CSDH patients.
Methods: We retrospectively included surgically treated CSDH patients between 2005 and 2019 in three hospitals in the Netherlands. The effect of the surgical approach to bilateral CSDH (unilateral vs. bilateral decompression) and anesthesia modality (general vs. local anesthesia) on outcome (complications, recurrence, and length of hospital stay over 4 days) was studied with logistic regression adjusting for potentially confounding radiological and clinical characteristics.
Results: Data of 1,029 consecutive patients were analyzed, mean age was 73.5 years (±11) and 75% of patients were male. Bilateral CSDH is independently associated with an increased risk of recurrence within 3 months in logistic regression analysis (aOR 1.7, 95% CI: 1.1-2.5) but recurrence rate did not differ between primary bilateral or unilateral decompression of bilateral CSDH. (15 vs. 17%, p = 0.775). Logistic regression analysis showed that general anesthesia was independently associated with an increased risk of complications (aOR 1.8, 95% CI: 1.0-3.3) and with a length of hospital admission of over 4 days (aOR 8.4, 95% CI: 5.6-12.4).
Conclusions: Bilateral CSDH is independently associated with higher recurrence rates. As recurrence rates in bilateral CSDH are similar for different surgical approaches, the optimal choice for primary bilateral decompression of bilateral CSDH could vary per patient. General anesthesia for surgical treatment of CSDH is associated with higher complication rates and longer hospital admission.

Gepubliceerd: Front Neurol. 2020;11:550.
Impact factor: 2.889; Q2

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4. The Role of Rituximab in Primary Central Nervous System Lymphoma
Bromberg JEC, van der Meulen M, Doorduijn JK.

Purpose of Review: The treatment of primary central nervous system lymphoma (PCNSL) is still under debate. One of the issues is the role of rituximab in improving the outcome. Here, we summarize the existing evidence, and comment on the literature on this topic.
Recent Findings: Two randomized controlled studies have been published recently, with conflicting results. Although the evidence of the benefit of rituximab is limited, it is already incorporated into many treatment regimens, both in studies and in standard clinical practice. The use of rituximab in PCNSL is still a matter of debate. A positive effect on the outcome is uncertain. However, there are no clinical signs of significantly increased toxicity. The uncertain positive effect should therefore be weighed against the increased costs of the treatment.

Gepubliceerd: Curr Oncol Rep. 2020;22(8):78.
Impact factor: 3.828; Q2

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5. Patients with mild traumatic brain injury and acute neck pain at the emergency department are a distinct category within the mTBI spectrum: a prospective multicentre cohort study
Coffeng SM, Jacobs B, de Koning ME, Hageman G, Roks G, van der Naalt J.

Background: Acute neck pain (ANP) has recently been demonstrated to be a predictor of persistent posttraumatic complaints after mild traumatic brain injury (mTBI). The aim of this study was to determine specific characteristics of patients with ANP following mTBI, their posttraumatic complaints and relationship with functional outcome.
Methods: Data from a prospective follow-up study of 922 mTBI patients admitted to the emergency department (ED) in three level-one trauma centres were analysed. Patients were divided into two groups: 156 ANP patients and 766 no acute neck pain (nANP) patients. Posttraumatic complaints were evaluated 2 weeks and 6 months post-injury using standardized questionnaires and functional outcome was evaluated at 6 months with the Glasgow Outcome Scale Extended (GOSE).
Results: ANP patients were more often female ($p < 0.01$), younger (38 vs. 47 years, $p < 0.01$) with more associated acute symptoms at the ED ($p < 0.05$) compared to nANP patients. More motor vehicle accidents (12% vs. 6%, $p = 0.01$) and less head wounds (58% vs. 73%, $p < 0.01$) in ANP patients indicated 'high-energy low-impact' trauma mechanisms. ANP patients showed more posttraumatic complaints 2 weeks and 6 months post-injury ($p < 0.05$) and more often incomplete recovery (GOSE < 8) was present after 6 months (56% vs. 40%, $p = 0.01$).
Conclusions: MTBI patients with acute neck pain at the ED constitute a distinct group within the mTBI spectrum with specific injury and demographic characteristics. Early identification of this at risk group already at the ED might allow specific and timely treatment to avoid development of incomplete recovery.

Gepubliceerd: BMC Neurol. 2020;20(1):315.
Impact factor: 2.356; Q3

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6. Spatiotemporal Dynamics of Single and Paired Pulse TMS-EEG Responses
de Goede AA, Cumplido-Mayoral I, van Putten M.

For physiological brain function a particular balance between excitation and inhibition is essential. Paired pulse transcranial magnetic stimulation (TMS) can estimate cortical excitability and the relative contribution of inhibitory and excitatory networks. Combining TMS with electroencephalography (EEG) enables additional assessment of the spatiotemporal dynamics of neuronal responses in the stimulated brain. This study aims to evaluate the spatiotemporal dynamics and stability of single and paired pulse TMS-EEG responses, and assess long intracortical inhibition (LICI) at the cortical level. Twenty-five healthy subjects were studied twice, approximately one week apart. Manual coil positioning was applied in sixteen subjects and robot-guided positioning in nine. Both motor cortices were stimulated with 50 single pulses and 50 paired pulses at each of the five interstimulus intervals (ISIs): 100, 150, 200, 250 and 300 ms. To assess stability and LICI, the intraclass correlation coefficient and cluster-based permutation analysis were used. We found great resemblance in the topographical distribution of the characteristic TMS-EEG components for single and paired pulse TMS. Stimulation of the dominant and non-dominant hemisphere resulted in a mirrored spatiotemporal dynamics. No significant effect on the TMS-EEG responses was found for either stimulated hemisphere, time or coil positioning method, indicating the stability of both single and paired pulse TMS-EEG responses. For all ISIs, LICI was characterized by significant suppression of the late N100 and P180 components in the central areas, without affecting the early P30, N45 and P60 components. These observations in healthy subjects can serve as reference values for future neuropsychiatric and pharmacological studies.

Gepubliceerd: Brain Topogr. 2020;33(4):425-37.
Impact factor: 2.759; Q2

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7. Conditional relative survival in primary central nervous system lymphoma: a population-based study in the Netherlands
Dinmohamed AG, van der Meulen M, Visser O, Doorduijn JK, Bromberg JEC.

Studies on conditional relative survival in primary central nervous system lymphoma (PCNSL) have hitherto been lacking in the literature. Using data from the Netherlands Cancer Registry, we examined the conditional 5-year relative survival up to 5-year postdiagnosis among PCNSL patients in the Netherlands. An encouraging finding of our study was that excess mortality decreased after each additional year survived postdiagnosis. However, on the other side of the pendulum, conditional 5-year relative survival did not exceed 95%. This finding indicates that PCNSL patients continue to experience substantial excess mortality, as compared to age- and sex-matched groups from the general population.

Gepubliceerd: Neurooncol Adv. 2020;2(1):vdaa133.

Impact factor: nvt; nvt

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8. Relevance of Somatosensory Evoked Potential Amplitude After Cardiac Arrest
Glimmerveen AB, Keijzer HM, Ruijter BJ, Tjepkema-Cloostermans MC, van Putten M, Hofmeijer J.

Objective: We present relations of SSEP amplitude with neurological outcome and of SSEP amplitude with EEG amplitude in comatose patients after cardiac arrest.
Methods: This is a post hoc analysis of a prospective cohort study in comatose patients after cardiac arrest. Amplitude of SSEP recordings obtained within 48-72 h, and EEG patterns obtained at 12 and 24h after cardiac arrest were related to good (CPC 1-2) or poor (CPC 3-5) outcome at 6 months. In 39% of the study population multiple SSEP measurements were performed. Additionally, SSEP amplitude was related to mean EEG amplitude.
Results: We included 138 patients (77% poor outcome). Absent SSEP responses, a N20 amplitude <0.4 μV within 48-72 h, and suppressed or synchronous EEG with suppressed background at 12 or 24 h after cardiac arrest were invariably associated with a poor outcome. Combined, these tests reached a sensitivity for prediction of poor outcome up to 58 at 100% specificity. N20 amplitude increased with a mean of 0.55 μV per day in patients with a poor outcome, and remained stable with a good outcome. There was no statistically significant correlation between SSEP and EEG amplitudes in 182 combined SSEP and EEG measurements (R (2) < 0.01).
Conclusions: N20 amplitude <0.4 μV is invariably associated with poor outcome. There is no correlation between SSEP and EEG amplitude. Significance: SSEP amplitude analysis may contribute to outcome prediction after cardiac arrest.

Gepubliceerd: Front Neurol. 2020;11:335.
Impact factor: 2.889; Q2

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9. Aerotoxic syndrome, discussion of possible diagnostic criteria
Hageman G, Pal TM, Nihom J, Mackenzie Ross SJ, van den Berg M.

Introduction: The term aerotoxic syndrome (ATS) was proposed 20 years ago to describe a constellation of symptoms reported by pilots and cabin crew following exposure to hydraulic fluids, engine oil, and pyrolysis products during flight. Hydraulic fluids and engine oil contain a large number of potentially toxic chemicals, including various organophosphate compounds (OPCs). However, ATS is not yet recognised as a valid diagnosis in aviation or general medicine, because the incidence and aetiology continues to be debated.
Discussion: Early studies report findings from symptom surveys or cognitive assessments of small samples of self-selected aircrew, but objective measures of exposure were lacking. Over the last decade, researchers have used more sophisticated techniques to measure exposure, such as on board monitoring studies and biomarkers of exposure (e.g., reduced levels of serum butyrylcholinesterases [BChE]) and more sophisticated techniques to detect nervous system injuries such as fMRI and autoantibody testing. Consideration has also been given to inter-individual

differences in the ability to metabolise certain chemical compounds as a result of genetic polymorphisms and exclusion of other potential causes of ill health.
Conclusions: We discuss factors which suggest a diagnosis of probable ATS; recommend an assessment protocol which incorporates the aforementioned techniques; and propose diagnostic criteria for probable ATS, based on our previously reported findings in aircrew and the results of recent studies.

Gepubliceerd: Clin Toxicol (Phila). 2020;58(5):414-6.
Impact factor: 3.659; Q1

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10. Three patients with probable aerotoxic syndrome
Hageman G, Pal TM, Nihom J, Mackenzie Ross SJ, van den Berg M.

Introduction: "Aerotoxic syndrome" is a debated entity. Regulatory authorities consider long-term health effects to be an unlikely consequence of exposure to contaminated air because several air quality monitoring studies report low concentrations of toxic chemicals in cabin air. We describe two pilots and one flight attendant, who developed ill health during their flying career which improved after cessation of flying.
Case details: The most frequently reported symptoms were headache, balance problems, fatigue, gastro-intestinal complaints and cognitive impairment. One of these patients had reduced levels of butyrylcholinesterase after a flight suggesting exposure to organophosphate compounds had occurred. All three were found to have elevated neuronal and glial auto-antibodies, biomarkers of central nervous system injury, and all three had genetic polymorphisms of paraoxonase (PON-1) and two of cytochrome P450, leading to a reduced ability to metabolize organophosphate compound (OPs).
Discussion: A similar constellation of symptoms has been described in other studies of aircrew, although objective evidence of exposure is lacking in most of these studies. Reduced levels of butyrylcholinesterases in one of our cases is suggestive of causation and elevated neuronal and glial autoantibodies provide objective evidence of damage to the central nervous system. We consider further research is warranted.

Gepubliceerd: Clin Toxicol (Phila). 2020;58(2):139-42.
Impact factor: 3.659; Q1

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11. Simplifying the clinical classification of polymerase gamma (POLG) disease based on age of onset; studies using a cohort of 155 cases
Hikmat O, Naess K, Engvall M, Klingenberg C, Rasmussen M, Tallaksen CM, Brodtkorb E, Ostergaard E, de Coo IFM, Pias-Peleteiro L, Isohanni P, Uusimaa J, Darin N, Rahman S, Bindoff LA.

Background: Variants in POLG are one of the most common causes of inherited mitochondrial disease. Phenotypic classification of POLG disease has evolved haphazardly making it complicated and difficult to implement in everyday clinical practise. The aim of our study was to simplify the classification and facilitate better clinical recognition.

Methods: A multinational, retrospective study using data from 155 patients with POLG variants recruited from seven European countries.
Results: We describe the spectrum of clinical features associated with POLG variants in the largest known cohort of patients. While clinical features clearly form a continuum, stratifying patients simply according to age of onset-onset prior to age 12 years; onset between 12 and 40 years and onset after the age of 40 years, permitted us to identify clear phenotypic and prognostic differences. Prior to 12 years of age, liver involvement (87%), seizures (84%), and feeding difficulties (84%) were the major features. For those with onset between 12 and 40 years, ataxia (90%), peripheral neuropathy (84%), and seizures (71%) predominated, while for those with onset over 40 years, ptosis (95%), progressive external ophthalmoplegia (89%), and ataxia (58%) were the major clinical features. The earlier the onset the worse the prognosis. Patients with epilepsy and those with compound heterozygous variants carried significantly worse prognosis.
Conclusion: Based on our data, we propose a simplified POLG disease classification, which can be used to guide diagnostic investigations and predict disease course.

Gepubliceerd: J Inherit Metab Dis. 2020;43(4):726-36.
Impact factor: 4.036; Q2

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12. The impact of gender, puberty, and pregnancy in patients with POLG disease

Hikmat O, Naess K, Engvall M, Klingenberg C, Rasmussen M, Tallaksen CME, Samsonsen C, Brodtkorb E, Ostergaard E, de Coo R, Pias-Peleteiro L, Isohanni P, Uusimaa J, Darin N, Rahman S, Bindoff LA.

Objective: To study the impact of gender, puberty, and pregnancy on the expression of POLG disease, one of the most common mitochondrial diseases known.
Methods: Clinical, laboratory, and genetic data were collected retrospectively from 155 patients with genetically confirmed POLG disease recruited from seven European countries. We used the available data to study the impact of gender, puberty, and pregnancy on disease onset and deterioration.
Results: We found that disease onset early in life was common in both sexes but there was also a second peak in females around the time of puberty. Further, pregnancy had a negative impact with 10 of 14 women (71%) experiencing disease onset or deterioration during pregnancy.
Interpretation: Gender clearly influences the expression of POLG disease. While onset very early in life was common in both males and females, puberty in females appeared associated both with disease onset and increased disease activity. Further, both disease onset and deterioration, including seizure aggravation and status epilepticus, appeared to be associated with pregnancy. Thus, whereas disease activity appears maximal early in life with no subsequent peaks in males, both menarche and pregnancy appear associated with disease onset or worsening in females. This suggests that hormonal changes may be a modulating factor.

Gepubliceerd: Ann Clin Transl Neurol. 2020;7(10):2019-25.
Impact factor: 3.660; Q2

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13. Delirium after cardiac arrest: Phenotype, prediction, and outcome
Keijzer HM, Klop M, van Putten M, Hofmeijer J.

Aim: To establish incidence, phenotype, long-term functional outcome, and early EEG predictors of delirium after cardiac arrest.
Methods: This is an ad hoc analysis of a prospective cohort study on outcome prediction of comatose patients after cardiac arrest. Patients with recovery of consciousness, who survived until hospital discharge, were subdivided in groups with and without delirium based on psychiatric consultation. Delirium phenotype and medical treatment were retrieved from patient files. All other data were prospectively collected. We used univariate analyses of baseline and early EEG characteristics for identification of possible delirium predictors. Association of delirium with neurological recovery at six months was analyzed with multinomial logistic regression analysis.
Results: Of 233 patients, 141 survived until hospital discharge, of whom 47 (33%) were diagnosed with delirium. There were no differences in baseline characteristics between patients with and without delirium. All delirious patients were treated with relatively high dosages of psychopharmaceuticals, mostly haloperidol and benzodiazepine agonists. Prevalent characteristics were disturbed cognition, perception and psychomotor functioning (98%). Half of the patients had language disorders or shouting. Delirium was associated with longer ICU and hospital admission, and more frequent discharge to rehabilitation centre or nursing home. There was a trend towards poorer neurological recovery. EEG measurements within 12 h after cardiac arrest could predict delirium with 91% specificity and 40% sensitivity.
Discussion: Delirium is common after cardiac arrest, and probably leads to longer hospitalization and poorer outcome. Optimal treatment is unclear. Early EEG holds potential to identify patients at risk.

Gepubliceerd: Resuscitation. 2020;151:43-9.
Impact factor: 4.215; Q1

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14. Differences in neurology residency training programmes across Europe - a survey among the Residents and Research Fellow Section of the European Academy of Neurology national representatives
Kleineberg NN, van der Meulen M, Franke C, Klingelhoefer L, Sauerbier A, Di Liberto G, Carvalho V, Berendse HW, Deuschl G.

Background and Purpose: Neurology is rapidly evolving as a result of continuous diagnostic and therapeutic progress, which influences the daily work of neurologists. Therefore, updating residency training programmes is crucial for the future of neurology. Several countries are currently discussing and/or modifying the structure of their neurology residency training programme. A detailed and up-to-date overview of the available European residency training programmes will aid this process.
Methods: A questionnaire addressing numerous aspects of residency training programmes in neurology was distributed among 38 national representatives of the Resident and Research Fellow Section of the European Academy of Neurology.
Results: We obtained data from 32 European countries (response rate 84%). The median (range) duration of the residency training programmes was 60 (12-72)

months. In the majority of countries, rotations to other medical disciplines were mandatory, mostly psychiatry (69%), internal medicine (66%) and neurosurgery (59%). However, the choice of medical fields and the duration of rotations varied substantially between countries. In 50% of countries, there were formal regulations regarding training in evidence-based medicine, teaching skills and/or leadership qualities. In many countries (75%), residents had to take an examination. **Conclusions:** We found substantial variation among European countries in the duration of residency training programmes, and especially in the choice of obligatory rotations to external medical disciplines. Despite a presumably similar spectrum of patients, neurology residency training programmes across Europe are not harmonized. The structure of the programme should be determined by its relevance for neurologists today and in the future.

Gepubliceerd: Eur J Neurol. 2020;27(8):1356-63.
Impact factor: 4.516; Q1

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15. A Pyramidal Cause of a Cerebellar Ataxia: HSP-7
Lagrand TJ, Hageman G.

A 43-year-old man presented with a slowly progressive fatigue and coordination problems, coupled with a radiological appearance of diffuse atrophy, especially in the cerebellar hemispheres. The diagnostic process was challenging because initially the additional investigations were focused on a cerebellar ataxia. In the following months, his ataxic gait developed in a more spastic pattern and whole exome sequencing revealed mutations in the SPG7 gene, confirming a diagnosis of hereditary spastic paraplegia. Therefore, the authors call for an extension of genetic panels in ataxia patients.

Gepubliceerd: Case Rep Neurol. 2020;12(3):329-33.
Impact factor: nvt; nvt

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16. Diagnostic value of serum biomarkers FGF21 and GDF15 compared to muscle sample in mitochondrial disease
Lehtonen JM, Auranen M, Darin N, Sofou K, Bindoff L, Hikmat O, Uusimaa J, Vieira P, Tulinius M, Lönnqvist T, de Coo IF, Suomalainen A, Isohanni P.

The aim of this study was to compare the value of serum biomarkers, fibroblast growth factor 21 (FGF21) and growth differentiation factor 15 (GDF15), with histological analysis of muscle in the diagnosis of mitochondrial disease. We collected 194 serum samples from patients with a suspected or known mitochondrial disease. Biomarkers were analyzed blinded using enzyme-labeled immunosorbent assay. Clinical data were collected using a structured questionnaire. Only 39% of patients with genetically verified mitochondrial disease had mitochondrial pathology in their muscle histology. In contrast, biomarkers were elevated in 62% of patients with genetically verified mitochondrial disease. Those with both biomarkers elevated had a muscle manifesting disorder and a defect affecting mitochondrial DNA expression. If at least one of the biomarkers was induced and the patient had a myopathic disease, a mitochondrial DNA expression disease was the cause with 94% probability. Among

patients with biomarker analysis and muscle biopsy taken <12 months apart, a mitochondrial disorder would have been identified in 70% with analysis of FGF21 and GDF15 compared to 50% of patients whom could have been identified with muscle biopsy alone. Muscle findings were nondiagnostic in 72% (children) and 45% (adults). Induction of FGF21 and GDF15 suggest a mitochondrial etiology as an underlying cause of a muscle manifesting disease. Normal biomarker values do not, however, rule out a mitochondrial disorder, especially if the disease does not manifest in muscle. We suggest that FGF21 and GDF15 together should be first-line diagnostic investigations in mitochondrial disease complementing muscle biopsy.

Gepubliceerd: J Inherit Metab Dis. 2020;44(2):469-80.
Impact factor: 4.036; Q2

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17. De Novo and Bi-allelic Pathogenic Variants in NARS1 Cause Neurodevelopmental Delay Due to Toxic Gain-of-Function and Partial Loss-of-Function Effects

Manole A, Efthymiou S, O'Connor E, Mendes MI, Jennings M, Maroofian R, Davagnanam I, Mankad K, Lopez MR, Salpietro V, Harripaul R, Badalato L, Walia J, Francklyn CS, Athanasiou-Fragkouli A, Sullivan R, Desai S, Baranano K, Zafar F, Rana N, Ilyas M, Horga A, Kara M, Mattioli F, Goldenberg A, Griffin H, Piton A, Henderson LB, Kara B, Aslanger AD, Raaphorst J, Pfundt R, Portier R, Shinawi M, Kirby A, Christensen KM, Wang L, Rosti RO, Paracha SA, Sarwar MT, Jenkins D, Ahmed J, Santoni FA, Ranza E, Iwaszkiewicz J, Cytrynbaum C, Weksberg R, Wentzensen IM, Guillen Sacoto MJ, Si Y, Telegrafi A, Andrews MV, Baldridge D, Gabriel H, Mohr J, Oehl-Jaschkowitz B, Debard S, Senger B, Fischer F, van Ravenwaaij C, Fock AJM, Stevens SJC, Bähler J, Nasar A, Mantovani JF, Manzur A, Sarkozy A, Smith DEC, Salomons GS, Ahmed ZM, Riazuddin S, Riazuddin S, Usmani MA, Seibt A, Ansar M, Antonarakis SE, Vincent JB, Ayub M, Grimmel M, Jelsig AM, Hjortshøj TD, Karstensen HG, Hummel M, Haack TB, Jamshidi Y, Distelmaier F, Horvath R, Gleeson JG, Becker H, Mandel JL, Koolen DA, Houlden H.

Aminoacyl-tRNA synthetases (ARSs) are ubiquitous, ancient enzymes that charge amino acids to cognate tRNA molecules, the essential first step of protein translation. Here, we describe 32 individuals from 21 families, presenting with microcephaly, neurodevelopmental delay, seizures, peripheral neuropathy, and ataxia, with de novo heterozygous and bi-allelic mutations in asparaginyl-tRNA synthetase (NARS1). We demonstrate a reduction in NARS1 mRNA expression as well as in NARS1 enzyme levels and activity in both individual fibroblasts and induced neural progenitor cells (iNPCs). Molecular modeling of the recessive c.1633C>T (p.Arg545Cys) variant shows weaker spatial positioning and tRNA selectivity. We conclude that de novo and bi-allelic mutations in NARS1 are a significant cause of neurodevelopmental disease, where the mechanism for de novo variants could be toxic gain-of-function and for recessive variants, partial loss-of-function.

Gepubliceerd: Am J Hum Genet. 2020;107(2):311-24.
Impact factor: 10.502; Q1

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18. Prediction of Persistent Impaired Glucose Tolerance in Patients with Minor Ischemic Stroke or Transient Ischemic Attack
Osei E, den Hertog HM, Fonville S, Brouwers P, Mulder L, Koudstaal PJ, Dippel DWJ, Zandbergen AAM, Lingsma HF.

Background: Impaired glucose tolerance (IGT) in patients with ischemic stroke can return to normal, reflecting an acute stress response, or persist. Persistent IGT is associated with an increased risk of recurrent stroke, other cardiovascular diseases and unfavorable outcome after stroke. We aim to validate our previously developed model to identify patients at risk of persistent IGT in an independent data set, and, if necessary, update the model.
Methods: The validation data set consisted of 239 nondiabetic patients with a minor ischemic stroke or TIA and IGT in the acute phase (2-hour post-load glucose levels between 7.8 and 11.0 mmol/l). The outcome was persistent versus normalized IGT, based on repeated oral glucose tolerance test after a median of 46 days. The discriminative ability of the original model was assessed with the area under the ROC curve (AUC). The updated model was internally validated with bootstrap resampling and cross-validated in the development population of the original model.
Results: One-hundred eighteen of 239 (49%) patients had persistent IGT. The original model, with the predictors age, current smoking, statin use, triglyceride, hypertension, history of cardiovascular diseases, body mass index (BMI), fasting plasma glucose performed poorly (AUC .60). The newly developed model included only BMI, hypertension, statin use, atrial fibrillation, 2-hour post-load glucose levels, HbA1c, large artery atherosclerosis, and predicted persistent IGT more accurately (internally validated AUC 0.66, externally validated AUC .71).
Conclusions: This prediction model with simple clinical variables can be used to predict persistent IGT in patients with IGT directly after minor stroke or TIA, and may be useful to optimize secondary prevention by early identification of patients with disturbed glucose metabolism.

Gepubliceerd: J Stroke Cerebrovasc Dis. 2020;29(6):104815.
Impact factor: 1.787; Q4

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19. The postictal state - What do we know?
Pottkämper JCM, Hofmeijer J, van Waarde JA, van Putten M.

This narrative review provides a broad and comprehensive overview of the most important discoveries on the postictal state over the past decades as well as recent developments. After a description and definition of the postictal state, we discuss postictal sypmtoms, their clinical manifestations, and related findings. Moreover, pathophysiological advances are reviewed, followed by current treatment options.

Gepubliceerd: Epilepsia. 2020;61(6):1045-61.
Impact factor: 6.040; Q1

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20. Standards of instrumentation of EMG
Tankisi H, Burke D, Cui L, de Carvalho M, Kuwabara S, Nandedkar SD, Rutkove S, Stålberg E, van Putten M, Fuglsang-Frederiksen A.

Standardization of Electromyography (EMG) instrumentation is of particular importance to ensure high quality recordings. This consensus report on "Standards of Instrumentation of EMG" is an update and extension of the earlier IFCN Guidelines published in 1999. First, a panel of experts in different fields from different geographical distributions was invited to submit a section on their particular interest and expertise. Then, the merged document was circulated for comments and edits until a consensus emerged. The first sections in this document cover technical aspects such as instrumentation, EMG hardware and software including amplifiers and filters, digital signal analysis and instrumentation settings. Other sections cover the topics such as temporary storage, trigger and delay line, averaging, electrode types, stimulation techniques for optimal and standardised EMG examinations, and the artefacts electromyographers may face and safety rules they should follow. Finally, storage of data and databases, report generators and external communication are summarized.

Gepubliceerd: Clin Neurophysiol. 2020;131(1):243-58.
Impact factor: 3.214; Q2

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21. Breath analysis in detecting epilepsy
van Dartel D, Schelhaas HJ, Colon AJ, Kho KH, de Vos CC.

The aim of this proof of concept study is to investigate if an electronic nose (eNose) is able to make a distinction between breath profiles of diagnosed epilepsy patients and epilepsy-free control subjects. An eNose is a non-invasive device, with a working mechanism that is based on the presence of volatile organic compounds (VOCs) in exhaled breath. These VOCs interact with the sensors of the eNose, and the eNose has to be trained to distinguish between breath patterns from patients with a specific disease and control subjects without that disease. During the measurement participants were asked to breathe through the eNose for five minutes via a disposable mouthpiece. Seventy-four epilepsy patients and 110 control subjects were measured to train the eNose and create a classification model. To assess the effects of anti-epileptic drugs (AEDs) usage on the classification, additional test groups were measured: seven patients who (temporarily) did not use AEDs and 11 patients without epilepsy who used AEDs. The results show that an eNose is able to make a distinction between epilepsy and control subjects with a sensitivity of 76%, a specificity of 67%, and an accuracy of 71%. The results of the two additional groups of subjects show that the created model classifies one out of seven epilepsy patients without AEDs and six out of 13 patients without epilepsy but with AEDs correctly. In this proof of concept study, the Aeonose(TM) is able to differentiate between epilepsy patients and control subjects. However, the number of false positives and false negatives is still high, which suggests that this first model is still mainly based on the usage of various AEDs.

Gepubliceerd: J Breath Res. 2020;14(3):031001.
Impact factor: 2.929; Q2

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22. An integrated perspective linking physiological and psychological consequences of mild traumatic brain injury
van der Horn HJ, Out ML, de Koning ME, Mayer AR, Spikman JM, Sommer IE, van der Naalt J.

Despite the often seemingly innocuous nature of a mild traumatic brain injury (mTBI), its consequences can be devastating, comprising debilitating symptoms that interfere with daily functioning. Currently, it is still difficult to pinpoint the exact cause of adverse outcome after mTBI. In fact, extensive research suggests that the underlying etiology is multifactorial. In the acute and early sub-acute stages, the pathophysiology of mTBI is likely to be dominated by complex physiological alterations including cellular injury, inflammation, and the acute stress response, which could lead to neural network dysfunction. In this stage, patients often report symptoms such as fatigue, headache, unstable mood and poor concentration. When time passes, psychological processes, such as coping styles, personality and emotion regulation, become increasingly influential. Disadvantageous, maladaptive, psychological mechanisms likely result in chronic stress which facilitates the development of long-lasting symptoms, possibly via persistent neural network dysfunction. So far, a systemic understanding of the coupling between these physiological and psychological factors that in concert define outcome after mTBI is lacking. The purpose of this narrative review article is to address how psychophysiological interactions may lead to poor outcome after mTBI. In addition, a framework is presented that may serve as a template for future studies on this subject.

Gepubliceerd: J Neurol. 2020;267(9):2497-506.
Impact factor: 3.956; Q1

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23. The additional value of an algorithm for atrial fibrillation at the stroke unit
van der Maten G, Plas GJJ, Meijs MFL, Brouwers P, Brusse-Keizer MGJ, den Hertog HM.

Background and Purpose: The rate of newly detected (paroxysmal) atrial fibrillation (AF) during inpatient cardiac telemetry is low. The objective of this study was to evaluate the additional diagnostic yield of an automated detection algorithm for AF on telemetric monitoring compared with routine detection by a stroke unit team in patients with recent ischemic stroke or TIA.
Methods: Patients admitted to the stroke unit of Medisch Spectrum Twente with acute ischemic stroke or TIA and no history of AF were prospectively included. All patients had telemetry monitoring, routinely assessed by the stroke unit team. The ST segment and arrhythmia monitoring (ST/AR) algorithm was active, with deactivated AF alarms. After 24 h the detections were analyzed and compared with routine evaluation.
Results: Five hundred and seven patients were included (52.5% male, mean age 70.2 ± 12.9 years). Median monitor duration was 24 (interquartile range 22-27) h. In 6 patients (1.2%) routine analysis by the stroke unit team concluded AF. In 24 patients (4.7%), the ST/AR Algorithm suggested AF. Interrater reliability was low (κ, 0.388, $p < 0.001$). Suggested AF by the algorithm turned out to be false positive in 11 patients. In 13 patients (2.6%) AF was correctly diagnosed by the algorithm. None of the cases detected by routine analysis were missed by the algorithm.

Conclusions: Automated AF detection during 24-h telemetry in ischemic stroke patients is of additional value to detect paroxysmal AF compared with routine analysis by the stroke unit team alone. Automated detections need to be carefully evaluated.

Gepubliceerd: J Stroke Cerebrovasc Dis. 2020;29(8):104930.
Impact factor: 1.787; Q4

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24. Health-related quality of life after chemotherapy with or without rituximab in primary central nervous system lymphoma patients: results from a randomised phase III study
van der Meulen M, Bakunina K, Nijland M, Minnema MC, Cull G, Stevens WBC, Baars JW, Mason KD, Beeker A, Beijert M, Taphoorn MJB, van den Bent MJ, Issa S, Doorduijn JK, Bromberg JEC, Dirven L.

Background: The impact of rituximab on health-related quality of life (HRQoL) in primary central nervous system lymphoma patients is not well known. We determined the impact of rituximab added to standard high-dose methotrexate-based treatment on HRQoL in patients in a large randomised trial. PATIENTS AND
Methods: Patients from a large phase III trial (HOVON 105/ALLG NHL 24), randomly assigned to receive standard chemotherapy with or without rituximab and followed by 30 Gy whole brain radiotherapy (WBRT) in patients ≤60 years, completed the EORTC QLQ-C30 and QLQ-BN20 questionnaires before and during treatment, and up to 24 months of follow-up or progression. Differences between treatment arms over time in global health status, role functioning, social functioning, fatigue, and motor dysfunction were assessed. Differences ≥10 points were deemed clinically relevant. The effect of WBRT on HRQoL was analysed in irradiated patients.
Results: A total of 160/175 patients eligible for the HRQoL study completed at least one questionnaire and were included. Over time, scores improved statistically significantly and were clinically relevant in both arms. Between arms, there were no differences on any scale (range: -3.8 to +4.0). Scores on all scales were improved to a clinically relevant extent at 12 and 24 months compared with baseline in both arms, except for fatigue and motor dysfunction at 12 months (-7.4 and -8.8, respectively). In irradiated patients (n = 59), scores in all preselected scales, except motor dysfunction, remained stable up to 24 months compared with shortly after WBRT, overall mean difference ranging between 0.02 and 4.570.
Conclusion: Compared with baseline, treatment resulted in improved HRQoL scores. The addition of rituximab to standard chemotherapy did not impact HRQoL over time. WBRT did not result in deterioration of HRQoL in the first 2 years.

Gepubliceerd: Ann Oncol. 2020;31(8):1046-55.
Impact factor: 18.274; Q1

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25. COVID-19 and neurological training in Europe: from early challenges to future perspectives
van der Meulen M, Kleineberg NN, Schreier DR, García-Azorin D, Di Lorenzo F.

The worldwide SARS-CoV-2 pandemic is dramatically affecting health systems with consequences also for neurological residency training. Here we report early

experiences and challenges that European neurologists and residents faced. The breadth of the pandemic and the social restrictions induced substantial modifications in both inpatient and outpatient clinical care and academic activities as well, adversely affecting our residency training. On the other hand we see also opportunities, such as gaining more clinical and professional skills. All these drastic and sudden changes lead us to reconsider some educational aspects of our training program that need to be improved in order to better prepare the neurologists of the future to manage unexpected and large emergency situations like the one we are living in these days. A reconsideration of the neurological training program could be beneficial to guarantee high standard level of the residency training in this period and beyond.

Gepubliceerd: Neurol Sci. 2020;41(12):3377-9.
Impact factor: 2.415; Q3

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26. Dopamine agonist treatment increases sensitivity to gamble outcomes in the hippocampus in de novo Parkinson's disease
van der Vegt JPM, Hulme OJ, Madsen KH, Buhmann C, Bloem BR, Münchau A, Helmich RC, Siebner HR.

Background: Parkinson's disease is associated with severe nigro-striatal dopamine depletion, leading to motor dysfunction and altered reward processing. We previously showed that drug-naïve patients with Parkinson's disease had a consistent attenuation of reward signalling in the mesolimbic and mesocortical system. Here, we address the neurobiological effects of dopaminergic therapy on reward sensitivity in the mesolimbic circuitry, and how this may contribute to neuropsychiatric symptoms.
Objectives: We tested the hypothesis that (1) dopaminergic treatment would restore the attenuated, mesolimbic and mesocortical responses to reward; and (2) restoration of reward responsivity by dopaminergic treatment would predict motor performance and the emergence of impulse control symptoms.
Methods: In 11 drug-naïve Parkinson patients, we prospectively assessed treatment-induced changes in reward processing before, and eight weeks after initiation of monotherapy with dopamine agonists. They were compared to 10 non-medicated healthy controls who were also measured longitudinally. We used whole-brain functional magnetic resonance imaging at 3 Tesla to assess the reward responsivity of the brain to monetary gains and losses, while participants performed a simple consequential gambling task.
Results: In patients, dopaminergic treatment improved clinical motor symptoms without significantly changing task performance. Dopamine agonist therapy induced a stronger reward responsivity in the right hippocampus with higher doses being less effective. None of the patients developed impulse control disorders in the follow-up period of four years.
Conclusions: Short-term treatment with first-ever dopaminergic medication partially restores deficient reward-related processing in the hippocampus in de novo Parkinson's disease.

Gepubliceerd: Neuroimage Clin. 2020;28:102362.
Impact factor: 4.350; Q2

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27. Using urine to diagnose large-scale mtDNA deletions in adult patients
Varhaug KN, Nido GS, de Coo I, Isohanni P, Suomalainen A, Tzoulis C, Knappskog P, Bindoff LA.

Objective: The aim of this study was to evaluate if urinary sediment cells offered a robust alternative to muscle biopsy for the diagnosis of single mtDNA deletions.
Methods: Eleven adult patients with progressive external ophthalmoplegia and a known single mtDNA deletion were investigated. Urinary sediment cells were used to isolate DNA, which was then subjected to long-range polymerase chain reaction. Where available, the patient`s muscle DNA was studied in parallel. Breakpoint and thus deletion size were identified using both Sanger sequencing and next generation sequencing. The level of heteroplasmy was determined using quantitative polymerase chain reaction.
Results: We identified the deletion in urine in 9 of 11 cases giving a sensitivity of 80%. Breakpoints and deletion size were readily detectable in DNA extracted from urine. Mean heteroplasmy level in urine was 38% ± 26 (range 8 - 84%), and 57% ± 28 (range 12 - 94%) in muscle. While the heteroplasmy level in urinary sediment cells differed from that in muscle, we did find a statistically significant correlation between these two levels (R = 0.714, P = 0.031(Pearson correlation)).
Interpretation: Our findings suggest that urine can be used to screen patients suspected clinically of having a single mtDNA deletion. Based on our data, the use of urine could considerably reduce the need for muscle biopsy in this patient group.

Gepubliceerd: Ann Clin Transl Neurol. 2020;7(8):1318-26.
Impact factor: 3.660; Q2

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28. Genetic screening in early-onset Alzheimer's disease identified three novel presenilin mutations
Wong TH, Seelaar H, Melhem S, Rozemuller AJM, van Swieten JC.

Mutations in presenilin 1 (PSEN1), presenilin 2 (PSEN2), and amyloid precursor protein (APP) are major genetic causes of early-onset Alzheimer's disease (EOAD). Clinical heterogeneity is frequently observed in patients with PSEN1 and PSEN2 mutations. Using whole exome sequencing, we screened a Dutch cohort of 68 patients with EOAD for rare variants in Mendelian Alzheimer's disease, frontotemporal dementia, and prion disease genes. We identified 3 PSEN1 and 2 PSEN2 variants. Three variants, 1 in PSEN1 (p.H21Profs*2) and both PSEN2 (p.A415S and p.M174I), were novel and absent in control exomes. These novel variants can be classified as probable pathogenic, except for PSEN1 (p.H21Profs*2) in which the pathogenicity is uncertain. The initial clinical symptoms between mutation carriers varied from behavioral problems to memory impairment. Our findings extend the mutation spectrum of EOAD and underline the clinical heterogeneity among PSEN1 and PSEN2 mutation carriers. Screening for Alzheimer's disease-causing genes is indicated in presenile dementia with an overlapping clinical diagnosis.

Gepubliceerd: Neurobiol Aging. 2020;86:201.e9-.e14.
Impact factor: 4.347; Q1

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29. Complications in cranioplasty after decompressive craniectomy: timing of the intervention
Goedemans T, Verbaan D, van der Veer O, Bot M, Post R, Hoogmoed J, Lequin MB, Buis DR, Vandertop WP, Coert BA, van den Munckhof P.

Objective: To prevent complications following decompressive craniectomy (DC), such as sinking skin flap syndrome, studies suggested early cranioplasty (CP). However, several groups reported higher complication rates in early CP. We studied the clinical characteristics associated with complications in patients undergoing CP, with special emphasis on timing.
Methods: A single-center observational cohort study was performed, including all patients undergoing CP from 2006 to 2018, to identify predictors of complications.
Results: 145 patients underwent CP: complications occurred in 33 (23%): 18 (12%) epi/subdural hemorrhage, 10 (7%) bone flap infection, 4 (3%) hygroma requiring drainage, and 1 (1%) post-CP hydrocephalus. On univariate analysis, acute subdural hematoma as etiology of DC, symptomatic cerebrospinal fluid (CSF) flow disturbance (hydrocephalus) prior to CP, and CP within three months after DC were associated with higher complication rates. On multivariate analysis, only acute subdural hematoma as etiology of DC (OR 7.5; 95% CI 1.9-29.5) and symptomatic CSF flow disturbance prior to CP (OR 2.9; 95% CI 1.1-7.9) were associated with higher complication rates. CP performed within three months after DC was not (OR 1.4; 95% CI 0.5-3.9). Pre-CP symptomatic CSF flow disturbance was the only variable associated with the occurrence of epi/subdural hemorrhage. (OR 3.8; 95% CI 1.6-9.0)
Conclusion: Cranioplasty has high complication rates, 23% in our cohort. Contrary to recent systematic reviews, early CP was associated with more complications (41%), explained by the higher incidence of pre-CP CSF flow disturbance and acute subdural hematoma as etiology of DC. CP in such patients should therefore be performed with highest caution.

Gepubliceerd: J Neurol. 2020;267(5):1312-20.
Impact factor: 3.956; Q1

Totale impact factor: 120.997
Gemiddelde impact factor: 4.127

Aantal artikelen 1e, 2e of laatste auteur: 15
Totale impact factor: 61.071
Gemiddelde impact factor: 4.071

Oogheelkunde

1. Rare metastatic seeding: endogenous endophtalmitis in Staphylococcus aureus sepsis
van der Weert S, Lansink PJ, Vermeijden JW, Cornet AD.

Gepubliceerd: Intensive Care Med. 2020;46(3):536-7.
Impact factor: 17.679; Q1

Totale impact factor: 17.679
Gemiddelde impact factor: 17.679

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 17.679
Gemiddelde impact factor: 17.679

Orthopedie

1. External iliac artery injury following total hip arthroplasty via the direct anterior approach-a case report
Burlage E, Gerbers JG, Geelkerken BRH, Verra WC.

Gepubliceerd: Acta Orthop. 2020;91(4):485-8.
Impact factor: 2.965; Q1

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2. Severe Hallux Valgus Angle Attended With High Incidence of Nonunion in Arthrodesis of the First Metatarsophalangeal Joint: A Follow-Up Study
Füssenich W, Brusse-Keizer MGJ, Somford MP.

The incidence of nonunion after first metatarsophalangeal joint (MTP-1) arthrodesis was found to be high in our clinic. By raising awareness for the problem, making a uniform surgical treatment protocol, banning the commonly used convex-concave reamers, and promoting solely the use of hand instruments to prepare the joint for arthrodesis, we tried to decrease the numbers of nonunion. This prospective cohort study included all patients who underwent MTP-1 fusion between January 2018 and March 2019. Patients were treated according to a standardized protocol, using hand instruments to prepare the joint for fusion. Anthropometric and therapy-related data were collected and compared with an earlier 2015-2016 cohort that was retrospectively assessed. Furthermore, the frequency of nonunion between convex-concave reamers and hand instruments was compared. A total of 53 patients underwent MTP-1 fusion surgery. The incidence of nonunion was 3.8%, significantly lower than the 24.1% in 2015 to 2016 (p = .002). Multivariate regression analysis showed a 7.11 times higher risk of nonunion in 2015 to 2016 compared with 2018 to 2019 (95% confidence interval [CI] 1.55 to 32.55) (p = .012). Furthermore, an increase of 10° in HVA showed a 1.52 risk of occurrence of nonunion (95% CI 1.07 to 2.17) (p = .021). The use of convex/concave reamers was univariately associated with a 3.61 times higher risk of nonunion (95% CI 1.14 to 11.43) (p = .029); however, after correction for preoperative HVA, the preparation method was no longer associated with the occurrence of nonunion (p = .108). Patients suffering from severe hallux valgus had nonunion in 32.1% of cases. Incidence of nonunion after MTP-1 arthrodesis was significantly reduced by raising awareness and by standardizing the treatment protocol. There was no significant difference in nonunion frequency between the methods of joint surface preparation. Severe hallux valgus is prone to nonunion, and more research into this indication for MTP-1 fusion and outcome is needed.

Gepubliceerd: J Foot Ankle Surg. 2020;59(5):993-6.
Impact factor: 1.043; Q4

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3. No differences in cost-effectiveness and short-term functional outcomes between cemented and uncemented total knee arthroplasty
Rassir R, Nolte PA, van der Lugt JCT, Nelissen R, Sierevelt IN, Verra WC.

Background: There is an ongoing debate regarding optimal fixation of total knee arthroplasty (TKA), however cost has not been addressed as profoundly. Therefore, the current study primarily aimed to compare costs and cost-effectiveness 1 year after cemented or uncemented TKA. A secondary objective was to compare short-term functional outcomes between both groups.
Methods: A posthoc prospective observational multicenter cohort study of 60 cemented and 50 uncemented Low Contact Stress (LCS) knee systems. Outcome was evaluated using the EuroQol5D-3 L (EQ5D) index, in order to calculate quality adjusted life years (QALYs). Total costs were calculated considering direct costs within the hospital setting (inpatient cost) as well as direct and indirect costs outside the hospital. Cost-effectiveness (total costs per QALY), Oxford Knee Score (OKS) and Numeric Rating Scale (NRS) were compared between cemented and uncemented cases at 1 year after surgery. HealthBASKET project, a micro-costing approach, represents the Dutch costs and situation and was used to calculate hospital stay. (In) direct costs outside the healthcare (medical cost and productivity cost) were determined using two validated questionnaires.
Results: Median costs per QALY were similar between cemented and uncemented TKA patients (€16,269 and €17,727 respectively; p = 0.50). Median OKS (44 and 42; p = 0.79), EQ5D (0.88 and 0.90; p = 0.82) and NRS for pain (1.0 and 1.0; p = 0.48) and satisfaction (9.0 and 9.0; p = 0.15) were also comparable between both groups.
Conclusion: For this type of knee implant (LCS), inpatient hospital costs and costs after hospitalization were comparable between groups.

Gepubliceerd: BMC Musculoskelet Disord. 2020;21(1):448.
Impact factor: 1.879; Q3

Totale impact factor: 5.887
Gemiddelde impact factor: 1.962

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 5.887
Gemiddelde impact factor: 1.962

Plastische chirurgie

1. Starting an autologous breast reconstruction program after plastic surgical training. Is it as good as it gets?
Beudeker N, Smits I, Spierings R, Rijntalder T, Verduijn PS, de Wit T, Mureau MA, Rakhorst HA.

Background: Today, the deep inferior epigastric perforator (DIEP) flap is considered to be the gold standard in microvascular breast reconstruction. Although this procedure is known as technically demanding, novice plastic surgeons must be able to perform these procedures to meet the rising demand. The purpose of this study was to evaluate if the young junior professional is trained adequately to set up and safely perform microsurgical breast reconstructions.
Methods: We compared outcomes of three identically trained novice plastic surgeons who introduced the DIEP flap in their working environment. Their hospitals differed in size and experience in microsurgery. Outcomes were compared between all start-ups and a center of excellence (EMC).
Results: A total of 152 DIEP flaps were performed in 123 patients among all start-ups together. Baseline characteristics and major complications were comparable between all groups. The total flap loss rate was 2% in the start-ups versus 3.9% in the control group ($p = 0.5$). Although there seems to be a trend in a longer operating time in both training and nontraining academic centers, no statistical significance was found between start-ups ($p = 0.13$) and the control group ($p = 0.17$). However, a learning curve seems to be present when it comes to duration of surgery and is greatest in the community centers with zero experience in microsurgery (ZGT $p = 0.002$, Amphia $p = 0.065$). The same accounts for hospital stay.
Conclusion: Although there seems to be a learning curve in terms of duration of surgery in hospitals with no experience in microsurgery, it is safe to perform microvascular breast reconstructions as a novice plastic surgeon.

Gepubliceerd: J Plast Reconstr Aesthet Surg. 2020;73(2):286-94.
Impact factor: 2.390; Q2

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2. Increased prevalence of BRCA1/2 mutations in women with macrotextured breast implants and anaplastic large cell lymphoma of the breast
de Boer M, Hauptmann M, Hijmering NJ, van Noesel CJM, Rakhorst HA, Meijers-Heijboer HEJ, de Boer JP, van der Hulst R, de Jong D, van Leeuwen FE.

Gepubliceerd: Blood. 2020;136(11):1368-72.
Impact factor: 17.794; Q1

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3. Breast Implant Prevalence in the Dutch Female Population Assessed by Chest Radiographs
de Boer M, van Middelkoop M, Hauptmann M, van der Bijl N, Bosmans JAW, Hendriks-Brouwer N, Schop SJ, de Boer JP, Hijmering NJ, Overbeek LIH, Lobbes MBI, Klazen CAH, de Jong D, Rakhorst HA, van der Hulst R, van Leeuwen FE.

Background: Breast implant-related health problems are a subject of fierce debate. Reliable population-based estimates of implant prevalence rates are not available, however, due to a lack of historical registries and incomplete sales data, precluding absolute risk assessments.
Objectives: This study aimed to describe the methodology of a novel procedure to determine Dutch breast implant prevalence based on the evaluation of routine chest radiographs.
Methods: The validity of the new method was first examined in a separate study. Eight reviewers examined a series of 180 chest radiographs with (n = 60) or without (n = 120) a breast implant confirmed by a computed tomography or magnetic resonance imaging scan. After a consensus meeting with best-performing expert reviewers, we reviewed 3000 chest radiographs of women aged 20 to 70 years in 2 large regional hospitals in the Netherlands in 2015. To calculate the national breast implant prevalence, regional prevalence variations were corrected utilizing the National Breast Cancer Screening Program.
Results: Eight reviewers scored with a median sensitivity of 71.7% (range, 41.7%-85.0%) and a median specificity of 94.6% (range, 73.4%-97.5%). After a consensus meeting and a reevaluation by best-performing expert reviewers, sensitivity was 79.9% and specificity was 99.2%. The estimated national prevalence of breast implants among women between 20 and 70 years was 3.0%, ranging from 1.7% at 21 to 30 years to 3.9% between 51 and 60 years.
Conclusions: The novel method in this study was validated with a high sensitivity and specificity, resulting in accurate prevalence estimates and providing the opportunity to conduct absolute risk assessment studies on the health consequences of breast implants.

Gepubliceerd: Aesthet Surg J. 2020;40(2):156-64.
Impact factor: 3.799; Q1

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4. Long-Term Health-Related Quality of Life after Four Common Surgical Treatment Options for Breast Cancer and the Effect of Complications: A Retrospective Patient-Reported Survey among 1871 Patients
Kouwenberg CAE, de Ligt KM, Kranenburg LW, Rakhorst H, de Leeuw D, Siesling S, Busschbach JJ, Mureau MAM.

Background: Differences in quality-of-life outcomes after different surgical breast cancer treatment options, including breast reconstruction, are relevant for counseling individual patients in clinical decision-making, and for (societal) evaluations such as cost-effectiveness analyses. However, current literature shows contradictory results, because of use of different patient-reported outcome measures and study designs with limited patient numbers. The authors set out to improve this evidence using patient-reported outcome measures in a large, cross-sectional study for different surgical breast cancer treatment options.
Methods: Quality of life was assessed through the EQ-5D-5L, European Organization for Research and Treatment of Cancer Quality of Life Questionnaires C30 and BR23, and the BREAST-Q. Patients with different treatments were compared after propensity-weighted adjustment of pretreatment differences. The EQ-5D was used to value the effect of surgical complications.

Results: A total of 1871 breast cancer patients participated (breast-conserving surgery, n = 615; mastectomy, n = 507; autologous reconstruction, n = 330; and implant-based reconstruction, n = 419). Mastectomy patients reported the lowest EQ-5D score (mastectomy, 0.805, breast-conserving surgery, 0.844; autologous reconstruction, 0.849; and implant-based reconstruction, 0.850) and functioning scores of the C30 questionnaire. On the BREAST-Q, autologous reconstruction patients had higher mean Satisfaction with Outcome, Satisfaction with Breasts, and Sexual Well-being scores than implant-based reconstruction patients. Complications in autologous reconstruction patients resulted in a substantially lower quality of life than in implant-based reconstruction patients.
Conclusions: This study shows the added value of breast conservation and reconstruction compared with mastectomy; however, differences among breast-conserving surgery, implant-based reconstruction, and autologous breast reconstruction were subtle. Complications resulted in poorer health-related quality of life.

Gepubliceerd: Plast Reconstr Surg. 2020;146(1):1-13.
Impact factor: 4.235; Q1

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5. 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. 2020;45(3):255-9.
Impact factor: 2.290; Q2

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6. Chromosome 20 loss is characteristic of breast implant-associated anaplastic large cell lymphoma
Los-de Vries GT, de Boer M, van Dijk E, Stathi P, Hijmering NJ, Roemer MGM, Mendeville M, Miedema DM, de Boer JP, Rakhorst HA, van Leeuwen FE, van der Hulst R, Ylstra B, de Jong D.

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a very rare type of T-cell lymphoma that is uniquely caused by a single environmental stimulus. Here, we present a comprehensive genetic analysis of a relatively large series of BIA-ALCL (n = 29), for which genome-wide chromosomal copy number aberrations (CNAs) and mutational profiles for a subset (n = 7) were determined. For comparison, CNAs for anaplastic lymphoma kinase (ALK)- nodal anaplastic large cell lymphomas

(ALCLs; n = 24) were obtained. CNAs were detected in 94% of BIA-ALCLs, with losses at chromosome 20q13.13 in 66% of the samples. Loss of 20q13.13 is characteristic of BIA-ALCL compared with other classes of ALCL, such as primary cutaneous ALCL and systemic type ALK+ and ALK- ALCL. Mutational patterns confirm that the interleukin-6-JAK1-STAT3 pathway is deregulated. Although this is commonly observed across various types of T-cell lymphomas, the extent of deregulation is significantly higher in BIA-ALCL, as indicated by phosphorylated STAT3 immunohistochemistry. The characteristic loss of chromosome 20 in BIA-ALCL provides further justification to recognize BIA-ALCL as a separate disease entity. Moreover, CNA analysis may serve as a parameter for future diagnostic assays for women with breast implants to distinguish seroma caused by BIA-ALCL from other causes of seroma accumulation, such as infection or trauma.

Gepubliceerd: Blood. 2020;136(25):2927-32.
Impact factor: 17.794; Q1

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7. Prospective assessment of function and cold-intolerance following revascularization for hypothenar hammer syndrome
Malsagova AT, van Burink MV, Smits ES, Zöphel OT, Stassen CM, Botman JMJ, Rakhorst HA.

Ulnar artery revascularization in hypothenar hammer syndrome has repeatedly been shown to reduce ischaemic symptoms, however with varying graft patency percentages. This study prospectively assesses the effect of revascularization surgery with a vein graft using validated questionnaires in seven patients. The Disabilities of the Arm, Shoulder and Hand (DASH) and the Cold Intolerance Symptom Severity (CISS) questionnaires have been used to compare the preoperative and postoperative functionality and cold intolerance. All patients showed improvement in either functionality, or cold intolerance, or both from disabled to nearly normalized levels and resumed their occupation at final follow-up (mean of 28 months). Strikingly this was also the case in a patient with graft stenosis. Patients with the highest preoperative questionnaire scores showed most postoperative improvement. In conclusion, revascularization surgery seems to improve the symptomatology irrespective of graft patency. Questionnaires can be a valuable contribution to quantify and to follow the symptomatology in hypothenar hammer syndrome.

Gepubliceerd: J Plast Reconstr Aesthet Surg. 2020;73(12):2164-70.
Impact factor: 2.390; Q2

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8. Introducing the virtual European Journal of Plastic Surgery Journal Club
Mayer HF, Reissis D, Rakhorst H, Perks G.

Gepubliceerd: European Journal of Plastic Surgery. 2020;43(4):363-4.
Impact factor: 0.159; Q4

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9. Have We Passed the Peak? The COVID-19 Plastic Surgery Webinar Pandemic

Navia A, Berner JE, Pereira N, Reissis D, Rakhorst H, Cuadra A.

Gepubliceerd: Aesthet Surg J. 2020;40(9):Np569-np73.
Impact factor: 3.799; Q1

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10. Postoperative Dorsal Proximal Interphalangeal Joint Subluxation in Volar Base Middle Phalanx Fractures
Oflazoglu K, Wilkens SC, Rakhorst H, Eberlin KR, Ring D, Chen NC.

Introduction: This study was designed to assess factors associated with postoperative dorsal proximal interphalangeal (PIP) joint subluxation after operative treatment of volar base middle phalanx fractures. Our second purpose was to study the association between postoperative dorsal subluxation with postoperative arthritis.
Materials and Methods: We identified 44 surgically treated volar base PIP joint fractures with available pre- and postoperative radiographs between 2002 and 2015 at two academic medical systems with a median follow-up of 3.5 months. Demographic, injury, radiographic, and treatment data that might be associated with postoperative dorsal subluxation were collected. Three hand surgeons independently assessed subluxation and arthritis on radiographs. Bivariate analysis was performed to analyze our two study purposes.
Results: Six of 44 (14%) had postoperative dorsal subluxation after initial surgery. Bivariate analysis showed no factors with statistically significant association with postoperative subluxation, assessed independently by three hand surgeons on radiographs. Fifty per cent of the joints with postoperative arthritis had postoperative subluxation compared with 21% of joints without postoperative subluxation. No significant association was found between postoperative dorsal subluxation with postoperative arthritis.
Conclusion: The association of persistent subluxation and early arthrosis in dorsal PIP joint fracture dislocations needs further study. At this time, it is unclear in what ways persistent subluxation or arthrosis affects the rate of reoperation. Level of Evidence This is a therapeutic level IV study.

Gepubliceerd: J Hand Microsurg. 2020;12(1):32-6.
Impact factor: nvt; nvt

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11. Toward International Harmonization of Breast Implant Registries: International Collaboration of Breast Registry Activities Global Common Data Set
Spronk PER, Begum H, Vishwanath S, Crosbie A, Earnest A, Elder E, Lumenta DB, Marinac-Dabic D, Moore CCM, Mureau MAM, Perks G, Pusic AL, Stark B, von Fritschen U, Klein H, Cooter RD, Rakhorst HA, Hopper I.

Background: The Poly Implant Prothèse incident and breast implant-associated anaplastic large cell lymphoma have pointed to the need for uniform registries for breast implants as key features to monitoring the outcomes of breast implant surgeries internationally. The purpose of this study was to identify and harmonize common data elements collected by breast implant registries across the International Collaboration of Breast Registry Activities (ICOBRA) global consortium.

Methods: The authors convened an international group of surgeons, consumers, nurses, registry experts, and regulators to review the data points. A modified Delphi approach was applied, to rate the importance of each point on a six-point Likert scale.
Results: Data points from six national breast implant registries were divided into categories: clinical, implant-related, patient-reported findings; operation details and implanting technique details; patient characteristics; unique device identifiers; unique patient identifiers; and clinical demographics. A total of 52 data points collected by over 33 percent of national registries were identified. After five rounds, 34 data points formed the final set with agreed definitions. The group recognized the critical importance of additional elements that are currently not uniformly collected (e.g., patient-reported outcomes and long-term data) and set out the process for the dynamic global set updates driven by evidence gaps.
Conclusions: The authors defined internationally agreed on common data elements and definitions used in breast implant registries. This collaboration will allow data sets to be combined, enabling an effective global early warning system of implant-related problems and further work on data sets.

Gepubliceerd: Plast Reconstr Surg. 2020;146(2):255-67.
Impact factor: 4.235; Q1

Totale impact factor: 58.885
Gemiddelde impact factor: 5.353

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 7.070
Gemiddelde impact factor: 2.357

Psychiatrie

1. New-generation drug-eluting coronary stents in octogenarians: Patient-level pooled analysis from the TWENTE I-IV trials
Ploumen EH, Buiten RA, Doggen CJM, Stoel MG, van Houwelingen KG, Schotborgh CE, Jessurun GAJ, Roguin A, Danse PW, Benit E, Aminian A, Linssen GCM, de Man F, Hartmann M, Buiten DG, Kok MM, Zocca P, von Birgelen C.

Background: Patients aged ≥80 years are often treated with new-generation drug-eluting stents (DES), but data from randomized studies are scarce owing to underrepresentation in most trials. We assessed 1-year clinical outcome of octogenarians treated with new-generation DES versus younger patients.
Methods: We pooled patient-level data of 9,204 participants in the TWENTE, DUTCH PEERS, BIO-RESORT, and BIONYX (TWENTE I-IV) randomized trials. The main clinical end point was target vessel failure (TVF), a composite of cardiac death, target vessel-related myocardial infarction (MI), or clinically indicated target vessel revascularization.
Results: The 671 octogenarian trial participants had significantly more comorbidities. TVF was higher in octogenarians than in 8,533 patients <80 years (7.3% vs 5.3%, hazard ratio [HR]: 1.36, 95% CI: 1.0-1.83, P = .04). The cardiac death rate was higher in octogenarians (3.9% vs 0.8%, P < .001). There was no significant between-group difference in target vessel MI (2.3% vs 2.3%, P = .88) and repeat target vessel revascularization (1.9% vs 2.8%, P = .16). In multivariate analyses, age ≥ 80 years showed no independent association with TVF (adjusted HR: 1.04, 95% CI: 0.76-1.42), whereas the risk of cardiac death remained higher in octogenarians (adjusted HR: 3.38, 95% CI: 2.07-5.52, P < .001). In 6,002 trial participants, in whom data on major bleeding were recorded, octogenarians (n = 459) showed a higher major bleeding risk (5.9% vs 1.9%; HR: 3.08, 95% CI: 2.01-4.74, P < .001).
Conclusions: Octogenarian participants in 4 large-scale randomized DES trials had more comorbidities and a higher incidence of the main end point TVF. Cardiac mortality was higher in octogenarians, whereas there was no increase in MI or target vessel revascularization rates. Treatment of octogenarian patients with new-generation DES appears to be safe and effective.

Gepubliceerd: Am Heart J. 2020;228:109-15.
Impact factor: 4.153; Q2

Totale impact factor: 4.135
Gemiddelde impact factor: 4.135

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

Radiologie

1. A patient-specific cerebral blood flow model
Helthuis JHG, van Doormaal TPC, Amin-Hanjani S, Du X, Charbel FT, Hillen B, van der Zwan A.

In clinical practice, many complex choices in treatment of complex cerebrovascular diseases have to be made. A patient-specific mathematical blood flow could aid these decisions. For certain cases, less accuracy is required and more simplistic models might be feasible. The current study is aiming to validate a patient-specific simplistic blood flow model in 20 healthy subjects. All subjects underwent MRI and Noninvasive Optimal Vessel Analysis (NOVA) to obtain patient-specific vascular morphology and flow measurements of all major cerebral arteries for validation. The mathematical model used was based on the Hagen-Poiseuille equations. Proximal boundary conditions were patient-specific blood pressure cuff measurements. For distal boundary conditions, a structured tree and a simple autoregulatory model were applied. Autoregulatory parameters were optimized based on the data of 10 additional healthy subjects. A median percentual flow difference of -3% (interquartile range -36% to 17%) was found. Regression analysis to an identity line resulted in R(2) values of 0.71 for absolute flow values. Bland-Altman plots showed a bias (levels of agreement) of 5% (-70 to 80%) for absolute flow. Based on these results the model proved to be accurate within a range that might be feasible for use in clinic. Major limitations to the model arise from the simplifications made compared to the actual physiological situation and limitations in the validation method. As the model is validated in healthy subjects only, further validation in actual patients is needed.

Gepubliceerd: J Biomech. 2020;98:109445.
Impact factor: 2.320; Q3

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2. Pulmonary involvement in primary Sjögren's syndrome, as measured by the ESSDAI
Heus A, Arends S, Van Nimwegen JF, Stel AJ, Nossent GD, Bootsma H.

Objective: Systemic features influence disease prognosis and choice of treatment in primary Sjögren's syndrome (pSS). Our aim was to investigate the prevalence of pulmonary involvement in pSS patients and to classify patients according to the pulmonary domain of the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI).
Methods: This retrospective cohort study included consecutive pSS patients, fulfilling American-European Consensus Group/American College of Rheumatology classification criteria, who visited the Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, in 2015. Data on pulmonary complaints and pulmonary tests were obtained from electronic patient records. Pulmonary involvement was recorded if therapy was needed or follow-up was recommended, and when it was possibly or assumed to be related to pSS instead of coincidental factors.
Results: Of the 262 included pSS patients, 88 (34%) had pulmonary complaints, mostly cough or dyspnoea on exertion. Pulmonary diagnostics were performed in 225

patients (86%). Pulmonary involvement was present and assumed to be related to pSS in 25 patients (10%) and possibly related to pSS in 14 (5%). Interstitial lung disease (ILD, n = 15), especially non-specific interstitial pneumonia (n = 7), was present most commonly. In total, 16 patients (6%) were scored as low (n = 4), moderate (n = 11), or high activity (n = 1) on the ESSDAI pulmonary domain.
Conclusion: In this cross-sectional study in daily clinical practice, pulmonary involvement was present in 10-15% of pSS patients, of which ILD was most common. Of all pSS patients, 6% were scored as active on the pulmonary domain of the ESSDAI.

Gepubliceerd: Scand J Rheumatol. 2020;49(1):38-46.
Impact factor: 3.025; Q3

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3. Are computed tomography-based measures of specific abdominal muscle groups predictive of adverse outcomes in older cancer patients?
Looijaard S, Maier AB, Voskuilen AF, Van Zanten T, Bouman DE, Klaase JM, Meskers CGM.

Purpose: It is unknown whether computed tomography (CT)-based total abdominal muscle measures are representative of specific abdominal muscle groups and whether analysis of specific abdominal muscle groups are predictive of the risk of adverse outcomes in older cancer patients.
Methods: Retrospective single-center cohort study in elective colon cancer patients aged ≥65 years. CT-based skeletal muscle (SM) surface area, muscle density and intermuscular adipose tissue (IMAT) surface area were determined for rectus abdominis; external- and internal oblique and transversus abdominis (lateral muscles); psoas; and erector spinae and quadratus lumborum (back muscles). Outcomes were defined as severe postoperative complications (Clavien-Dindo score >2) and long-term survival (median follow-up 5.2 years).
Results: 254 older colon cancer patients were included (median 73.6 years, 62.2% males). Rectus abdominis showed the lowest SM surface area and muscle density and the back muscles showed the highest IMAT surface area. Psoas muscle density, and lateral muscle density and percentage IMAT were associated with severe postoperative complications independent of gender, age and cancer stage.
Conclusions: CT-based total abdominal muscle quantity and quality do not represent the heterogeneity that exists between specific muscle groups. The potential added value of analysis of specific muscle groups in predicting adverse outcomes in older (colon) cancer patients should be further addressed in prospective studies.

Gepubliceerd: Heliyon. 2020;6(11):e05437.
Impact factor: nvt; nvt

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4. Computed Tomography-Based Body Composition Is Not Consistently Associated with Outcome in Older Patients with Colorectal Cancer
Looijaard S, Meskers CGM, Slee-Valentijn MS, Bouman DE, Wymenga ANM, Klaase JM, Maier AB.

Background: Current literature is inconsistent in the associations between computed tomography (CT)-based body composition measures and adverse outcomes in older patients with colorectal cancer (CRC). Moreover, the associations with consecutive treatment modalities have not been studied. This study compared the associations of CT-based body composition measures with surgery- and chemotherapy-related complications and survival in older patients with CRC. MATERIALS AND
Methods: A retrospective single-center cohort study was conducted in patients with CRC aged ≥65 years who underwent elective surgery between 2010 and 2014. Gender-specific standardized scores of preoperative CT-based skeletal muscle (SM), muscle density, intermuscular adipose tissue (IMAT), visceral adipose tissue (VAT), subcutaneous adipose tissue, IMAT percentage, SM/VAT, and body mass index (BMI) were tested for their associations with severe postoperative complications, prolonged length of stay (LOS), readmission, and dose-limiting toxicity using logistic regression and 1-year and long-term survival (range 3.7-6.6 years) using Cox regression. Bonferroni correction was applied to account for multiple testing.
Results: The study population consisted of 378 patients with CRC with a median age of 73.4 (interquartile range 69.5-78.4) years. Severe postoperative complications occurred in 13.0%, and 39.4% of patients died during follow-up. Dose-limiting toxicity occurred in 77.4% of patients receiving chemotherapy (n = 53). SM, muscle density, VAT, SM/VAT, and BMI were associated with surgery-related complications, and muscle density, IMAT, IMAT percentage, and SM/VAT were associated with long-term survival. After Bonferroni correction, no CT-based body composition measure was significantly associated with adverse outcomes. Higher BMI was associated with prolonged LOS.
Conclusion: The associations between CT-based body composition measures and adverse outcomes of consecutive treatment modalities in older patients with CRC were not consistent or statistically significant.
Implications for Practice: Computed tomography (CT)-based body composition, including muscle mass, muscle density, and intermuscular, visceral, and subcutaneous adipose tissue, showed inconsistent and nonsignificant associations with surgery-related complications, dose-limiting toxicity, and overall survival in older adults with colorectal cancer. This study underscores the need to verify whether CT-based body composition measures are worth implementing in clinical practice.

Gepubliceerd: Oncologist. 2020;25(3):e492-e501.
Impact factor: 5.025; Q2

Totale impact factor: 10.370
Gemiddelde impact factor: 2.593

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 5.345
Gemiddelde impact factor: 2.673

Radiotherapie

1. Randomized controlled trial to identify the optimal radiotherapy scheme for palliative treatment of incurable head and neck squamous cell carcinoma
Al-Mamgani A, Kessels R, Verhoef CG, Navran A, Hamming-Vrieze O, Kaanders J, Steenbakkers R, Tans L, Hoebers F, Ong F, van Werkhoven E, Langendijk JA.

Background: No randomized controlled trials (RCT) have yet identified the optimal palliative radiotherapy scheme in patients with incurable head and neck squamous cell carcinoma (HNSCC). We conducted RCT to compare two radiation schemes in terms of efficacy, toxicity and quality-of-life (QoL).
Materials and Methods: Patients with locally-advanced HNSCC who were ineligible for radical treatment and those with limited metastatic disease were randomly assigned in 1:1 ratio to arm 1 (36 Gy in 6 fractions, twice a week) or arm 2 (50 Gy in 16 fractions, four times a week).
Results: The trial was discontinued early because of slow accrual (34 patients enrolled). Objective response rates were 38.9% and 57.1% for arm 1 and 2 respectively (p = 0.476). The median time to loco-regional progression was not reached. The loco-regional control rates at 1 year was 57.4% and 69.3% in arm 1 and 2 (p = 0.450, HR = 0.56, 95%CI 0.12-2.58). One-year overall survival was 33.3% and 57.1%, with medians of 35.4 and 59.5 weeks, respectively (p = 0.215, HR = 0.55, 95%CI 0.21-1.43). Acute grade ≥3 toxicity was lower in arm 1 (16.7% versus 57.1%, p = 0.027), with the largest difference in grade 3 mucositis (5.6% versus 42.9%, p = 0.027). However, no significant deterioration in any of the patient-reported QoL-scales was found.
Conclusion: No solid conclusion could be made on this incomplete study which is closed early. Long-course radiotherapy did not show significantly better oncologic outcomes, but was associated with more acute grade 3 mucositis. No meaningful differences in QoL-scores were found. Therefore, the shorter schedule might be carefully advocated. However, this recommendation should be interpreted with great caution because of the inadequate statistical power.

Gepubliceerd: Radiother Oncol. 2020;149:181-8.
Impact factor: 4.856; Q1

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2. Prognostic Integrated Image-Based Immune and Molecular Profiling in Early-Stage Endometrial Cancer
Horeweg N, de Bruyn M, Nout RA, Stelloo E, Kedziersza K, León-Castillo A, Plat A, Mertz KD, Osse M, Jürgenliemk-Schulz IM, Lutgens L, Jobsen JJ, van der Steen-Banasik EM, Smit VT, Creutzberg CL, Bosse T, Nijman HW, Koelzer VH, Church DN.

Optimum risk stratification in early-stage endometrial cancer combines clinicopathologic factors and the molecular endometrial cancer classification defined by The Cancer Genome Atlas (TCGA). It is unclear whether analysis of intratumoral immune infiltrate improves this. We developed a machine-learning, image-based algorithm to quantify density of CD8(+) and CD103(+) immune cells in tumor epithelium and stroma in 695 stage I endometrioid endometrial cancers from the PORTEC-1 and -2 trials. The relationship between immune cell density and

clinicopathologic/molecular factors was analyzed by hierarchical clustering and multiple regression. The prognostic value of immune infiltrate by cell type and location was analyzed by univariable and multivariable Cox regression, incorporating the molecular endometrial cancer classification. Tumor-infiltrating immune cell density varied substantially between cases, and more modestly by immune cell type and location. Clustering revealed three groups with high, intermediate, and low densities, with highly significant variation in the proportion of molecular endometrial cancer subgroups between them. Univariable analysis revealed intraepithelial CD8(+) cell density as the strongest predictor of endometrial cancer recurrence; multivariable analysis confirmed this was independent of pathologic factors and molecular subgroup. Exploratory analysis suggested this association was not uniform across molecular subgroups, but greatest in tumors with mutant p53 and absent in DNA mismatch repair-deficient cancers. Thus, this work identified that quantification of intraepithelial CD8(+) cells improved upon the prognostic utility of the molecular endometrial cancer classification in early-stage endometrial cancer.

Gepubliceerd: Cancer Immunol Res. 2020;8(12):1508-19.
Impact factor: 8.728; Q1

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3. Internal mammary and medial supraclavicular lymph node chain irradiation in stage I-III breast cancer (EORTC 22922/10925): 15-year results of a randomised, phase 3 trial
Poortmans PM, Weltens C, Fortpied C, Kirkove C, Peignaux-Casasnovas K, Budach V, van der Leij F, Vonk E, Weidner N, Rivera S, van Tienhoven G, Fourquet A, Noel G, Valli M, Guckenberger M, Koiter E, Racadot S, Abdah-Bortnyak R, Van Limbergen EF, Engelen A, De Brouwer P, Struikmans H, Bartelink H.

Background: 10-year results from several studies showed improved disease-free survival and distant metastasis-free survival, reduced breast cancer-related mortality, and variable effects on overall survival with the addition of partial or comprehensive regional lymph node irradiation after surgery in patients with breast cancer. We present the scheduled 15-year analysis of the European Organisation for Research and Treatment of Cancer (EORTC) 22922/10925 trial, which aims to investigate the impact on overall survival of elective internal mammary and medial supraclavicular (IM-MS) irradiation.
Methods: EORTC 22922/10925, a randomised, phase 3 trial done across 46 radiation oncology departments from 13 countries, included women up to 75 years of age with unilateral, histologically confirmed, stage I-III breast adenocarcinoma with involved axillary nodes or a central or medially located primary tumour. Surgery consisted of mastectomy or breast-conserving surgery and axillary staging. Patients were randomly assigned (1:1) centrally using minimisation to receive IM-MS irradiation at 50 Gy in 25 fractions (IM-MS irradiation group) or no IM-MS irradiation (control group). Stratification was done for institution, menopausal status, site of the primary tumour within the breast, type of breast and axillary surgery, and pathological T and N stage. Patients and investigators were not masked to treatment allocation. The primary endpoint was overall survival analysed according to the intention-to-treat principle. Secondary endpoints were disease-free survival, distant metastasis-free survival, breast cancer mortality, any breast cancer recurrence, and cause of death.

Follow-up is ongoing for 20 years after randomisation. This study is registered with ClinicalTrials.gov, NCT00002851.
Findings: Between Aug 5, 1996, and Jan 13, 2004, we enrolled 4004 patients, of whom 2002 were randomly assigned to the IM-MS irradiation group and 2002 to the no IM-MS irradiation group. At a median follow-up of 15·7 years (IQR 14·0-17·6), 554 (27·7%) patients in the IM-MS irradiation group and 569 (28·4%) patients in the control group had died. Overall survival was 73·1% (95% CI 71·0-75·2) in the IM-MS irradiation group and 70·9% (68·6-72·9) in the control group (HR 0·95 [95% CI 0·84-1·06], p=0·36). Any breast cancer recurrence (24·5% [95% CI 22·5-26·6] vs 27·1% [25·1-29·2]; HR 0·87 [95% CI 0·77-0·98], p=0·024) and breast cancer mortality (16·0% [14·3-17·7] vs 19·8% [18·0-21·7]; 0·81 [0·70-0·94], p=0·0055) were lower in the IM-MS irradiation group than in the control group. No significant differences in the IM-MS irradiation group versus the control group were seen for disease-free survival (60·8% [95% CI 58·4-63·2] vs 59·9% [57·5-62·2]; HR 0·93 [95% CI 0·84-1·03], p=0·18), or distant metastasis-free survival (70·0% [67·7-72·2] vs 68·2% [65·9-70·3]; 0·93 [0·83-1·04], p=0·18). Causes of death between groups were similar.
Interpretation: The 15-year results show a significant reduction of breast cancer mortality and any breast cancer recurrence by IM-MS irradiation in stage I-III breast cancer. However, this is not converted to improved overall survival.
Funding: US National Cancer Institute, Ligue Nationale contre le Cancer, and KWF Kankerbestrijding.

Gepubliceerd: Lancet Oncol. 2020;21(12):1602-10.
Impact factor: 33.752; Q1

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4. Dexamethasone for the Prevention of a Pain Flare After Palliative Radiation Therapy for Painful Bone Metastases: The Multicenter Double-Blind Placebo-Controlled 3-Armed Randomized Dutch DEXA Study
van der Linden YM, Westhoff PG, Stellato RK, van Baardwijk A, de Vries K, Ong F, Wiggenraad R, Bakri B, Wester G, de Pree I, van Veelen L, Budiharto T, Schippers M, Reyners AKL, de Graeff A.

Purpose: After radiation therapy for painful bone metastases, up to 44% of patients report a pain flare (PF). Our study compared 2 dose schedules of dexamethasone versus placebo to prevent PF.
Methods and Materials: This double-blind, randomized, placebo-controlled trial allocated patients with painful bone metastases from solid tumors randomly to receive 8 mg dexamethasone before radiation therapy followed by 3 daily doses (group A), 8 mg dexamethasone followed by 3 doses of placebo (group B), or 4 doses of placebo (group C). Patients reported worst pain scores, study medication side effects, and opioid intake before treatment and thereafter daily for 14 days and on day 28. PF was defined as at least a 2-point increase on a 0 to 10 pain scale with no decrease in opioid intake or a 25% or greater increase in opioid intake with no decrease in pain score, followed by a return to baseline or lower. The primary analysis was by intention to treat with patients who had missing data classified as having a PF.
Results: From January 2012 to April 2016, 295 patients were randomized. PF incidence was 38% for group A, 27% for group B, and 39% for group C (P = .07). Although patients in group B had the lowest PF incidence, a relatively high percentage did not return to baseline pain levels, indicating pain progression. The

mean duration of PF was 2.1 days for group A, 4.5 days for group B, and 3.3 days for group C (P = .0567). Dexamethasone postponed PF occurrence; in group A 52% occurred on days 2 to 5 versus 73% in group B and 99% in group C (P = .02). Patients in group A reported lower mean pain scores on days 2 to 5 than those in group B or C (P < .001). Side effects were similar.
Conclusions: There was insufficient evidence that dexamethasone reduced the incidence of radiation-induced PF. However, dexamethasone postponed the occurrence of PF and led to lower mean pain scores on days 2 to 5.

Gepubliceerd: Int J Radiat Oncol Biol Phys. 2020;108(3):546-53.
Impact factor: 5.859; Q1

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5. The Mitotic Activity Index in combination with Her2neu: a strong prognosticator in breast cancer
Jobsen JJ, Struikmans H, van der Palen J, Siemerink E.

Purpose: The aim of this study is to evaluate the prognostic value of the Mitotic Activity Index (MAI) in combination with the human epidermal growth factor receptor (Her2) for distant metastases-free survival (DMFS) and disease-specific survival (DSS) in breast cancer and compare it with the immunohistochemically (IHC) profile types.
Methods: Analyses were based on 2.923 breast-conserving breast cancer specimens with known MAI, Her2 status, and hormone receptor status, resulting in 2.678 Her2MAI combinations, MAI ≤ 12/Her2negative, MAI > 12/Her2negative, MAI > 12/Her2positive, and MAI ≤ 12/Her2positive, and 2.560 IHC profile types, luminal A, luminal B, triple negative, and non-luminal Her2positive.
Results: For DMFS, the MAI > 12/Her2negative combination showed a significantly worse outcome in multivariate analyses compared to the MAI ≤ 12/Her2negative combination. None of the IHC profile types showed significantly different outcomes for DMFS and DSS as compared to luminal A. We performed a separate analysis on age and lymph node status. The significance of MAI > 12/Her2negative seems to be limited to women ≤ 55 years for both DMFS and DSS. However, with respect to DSS, this seems to be limited to node negative cases. The IHC profile types for DSS, luminal B showed a significantly worse outcome for women > 55 years compared to that for luminal A, although it showed rather wide confidence interval.
Conclusion: The MAI > 12/Her2negative combination seems to be a strong prognosticator for DMFS and DSS, particularly for women ≤ 55 years. However, none of the IHC profile types seems to be a prognosticator in breast cancer.

Gepubliceerd: Breast Cancer Res Treat. 2020;181(1):13-21.
Impact factor: 3.831; Q2

Totale impact factor: 57.026
Gemiddelde impact factor: 11.405

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 3.831
Gemiddelde impact factor: 0

Reumatologie

1. A goal management intervention for patients with polyarthritis and elevated levels of depressive symptoms: a quasiexperimental study
Arends RY, Bode C, Taal E, Van de Laar M.

Purpose: Goal was to establish whether an intervention that aims to increase goal management competencies is effective in decreasing elevated levels of depressive symptoms and increasing well-being in patients with polyarthritis.
Materials and methods: Eighty-five persons with polyarthritis and elevated levels of depressive symptoms participated in the goal management intervention consisting of six group-based meetings. A quasiexperimental design with baseline measurement, follow-up at 6 months and a reference group of 151 patients from an observational study was applied. Primary outcome was depression; secondary outcomes were anxiety, purpose in life, positive affect, satisfaction with participation, goal management strategies, and arthritis self-efficacy. A linear mixed model procedure was applied to evaluate changes in outcomes.
Results: No improvement was found for depressive symptoms and no changes were found for the secondary outcomes, except for positive affect that improved in the intervention group. This increase was mediated by an increase in goal adjustment. Furthermore, goal maintenance decreased and self-efficacy for other symptoms increased in the intervention group.
Conclusion: This study indicates that interventions designed to aid patients with arthritis with goal management skills are potentially helpful for increasing positive affect, although further studies are needed.Implications for rehabilitationPeople with polyarthritis have to manage their disease in combination with possibly conflicting roles and personal goals, resulting in an ongoing process of finding equilibrium in a constantly changing situation.Based on a person-focused view, the program Right on Target focused on coping with threatened activities and life goals due to arthritis.The program consisted of six group-based meetings led by a trained nurse and a personal trajectory wherein participants were stimulated to try out various behavioral options related to an own threatened activity in concordance with their personal goals.The program seemed effective in increasing flexible goal adjustment and self-efficacy and participants experienced more positive affect directly after the program and at 6-month follow-up.

Gepubliceerd: Disabil Rehabil. 2020;42(7):957-66.
Impact factor: 2.222; Q1

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2. Validation and implementation of a patient-reported experience measure for patients with rheumatoid arthritis and spondyloarthritis in the Netherlands
Beckers E, Webers C, Boonen A, Ten Klooster PM, Vonkeman HE, van Tubergen A.

Objectives: To test the psychometric properties of the United Kingdom's Commissioning for Quality in Rheumatoid Arthritis Patient-Reported Experience Measure (CQRA-PREM) in patients with spondyloarthritis (SpA) and rheumatoid arthritis (RA) and to implement this questionnaire in daily practice in the Netherlands.

Methods: After a forward-backward translation procedure into Dutch, the CQRA-PREM was tested into two quality registries in daily practice. Face validity was assessed with focus group interviews. Feasibility was evaluated through completion times and interpretability of domain scores through floor and ceiling effects. Internal consistency (Cronbach's α coefficients) and homogeneity (corrected item-total correlations) were determined. Divergent validity was assessed by Spearman's rank correlation coefficients (r(s)) between the average scores of domains and outcome measures. The CQRA-PREM was implemented in daily practice, and the results were used in quality improvement cycles.
Results: Face validity of the CQRA-PREM was good. The CQRA-PREM was completed by 282 patients with SpA and 376 with RA. Median time to complete the CQRA-PREM was 4.7 min. Ceiling effects were found in three out of seven domains. Internal consistency of nearly all domains was considered good ($0.65 \leq \alpha \leq 0.95$). Thresholds for homogeneity were exceeded within three domains ($r(p) > 0.7$), suggesting item redundancy. Divergent validity showed that nearly all domains of the CQRA-PREM were at most weakly correlated with outcomes measures ($-0.3 \leq r(s) \leq 0.3$). The CQRA-PREM could identify areas of improvement for providing patient-centered care.
Conclusion: The CQRA-PREM has acceptable psychometric properties and has shown to be a useful tool in evaluating quality of care from the patients' perspective in the Netherlands.
Trial registration: SpA-Net is registered in the Netherlands Trial Registry (NTR6740).

Gepubliceerd: Clin Rheumatol. 2020;39(10):2889-97.
Impact factor: 2.394; Q3

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3. Frequency of real-world reported adverse drug reactions in rheumatoid arthritis patients
Giraud EL, Jessurun NT, van Hunsel F, van Puijenbroek EP, van Tubergen A, Ten Klooster PM, Vonkeman HE.

Objectives: To describe the cumulative incidences of adverse drug reactions (ADRs) associated with disease-modifying anti-rheumatic drugs (DMARDs) in rheumatoid arthritis (RA) patients from real-world data (RWD), using the DREAM-RA registry, and to compare these with incidence frequencies mentioned in the Summary of Product Characteristics (SmPC).
Methods: All ADRs in patients with recorded use of adalimumab, etanercept, hydroxychloroquine, leflunomide, oral and subcutaneous methotrexate, and sulfasalazine from a single center participating in the DREAM-RA registry (n = 1,098 patients) that were directly sent to the Netherlands Pharmacovigilance Center Lareb were assessed. Cumulative incidences were calculated, described and compared to the most recently revised SmPCs.
Results: In total, 14 ADRs (≥5 case reports) associated with the use of one of the included DMARDs were reported with a higher estimated cumulative incidence compared to the SmPC. For hydroxychloroquine and sulfasalazine, 5 ADRs (≥5 case reports) mentioned with an 'unknown' incidence in the SmPC were reported as 'common' in this study.

Conclusions: Although ADR data in the DREAM-RA registry were partly comparable with data in the SmPCs, RWD from this patient registry provided an added value to the currently available information on the incidences of ADRs associated with DMARDs in RA patients as described in SmPCs.

Gepubliceerd: Expert Opin Drug Saf. 2020;19(12):1617-24.
Impact factor: 3.383; Q2

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4. Stakeholders' perspectives on a patient-reported outcome measure-based drug safety monitoring system for immune-mediated inflammatory diseases
Kosse LJ, Jessurun NT, Vonkeman HE, Tas SW, Nurmohamed MT, Hoentjen F, van Doorn MBA, van Puijenbroek EP, van den Bemt BJF, de Vries M.

Background: Biologics are used as effective therapeutics to treat a variety of diseases. Even though biologics are widely used, knowledge on the post-marketing experience of patients is limited. Therefore, a framework was established for a patient-reported outcome measure (PROM)-based drug safety monitoring system for ADRs attributed to biologics, known as the 'Dutch Biologic Monitor'.
Objective: Generation of a multi-stakeholder perspective on the preferred setup, potential and added value of a PROM-based national drug safety monitoring system.
Methods: Nineteen stakeholders were interviewed following a structured interview guide. Transcribed data were coded and analyzed to count frequencies and to generate recurring themes.
Results: Stakeholders (84.2%) support the establishment of a national drug safety monitoring system, but the feasibility depends on the implementation process. The need for integration and assessment of PROMs on ADRs in clinical practice and the preference to monitor small molecules and new drugs were emphasized. Preferably, all pharmacological options per indication should be monitored.
Conclusions: Stakeholders recommend to establish a PROM-based national drug safety monitoring system focused on ADRs attributed to biologics, small molecules, and new drugs. Moreover, PROMs on ADRs ideally need to become integrated in clinical practice to provide health-care providers more insight in patients' perspectives.

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Impact factor: 3.383; Q2

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5. Immune-mediated inflammatory disease patients' preferences in adverse drug reaction information regarding biologics
Kosse LJ, Weits G, Vonkeman HE, Spuls PI, Van Den Bemt BJF, Tas SW, Hoentjen F, Nurmohamed MT, Van Doorn MBA, Van Puijenbroek EP, Jessurun NT.

Objectives: Patient-reported outcomes (PROs) are increasingly used in studies and medical practice to obtain information on patients' perspectives toward their treatment or disease. However, most study outcomes are primarily directed at healthcare professionals. It was aimed to obtain insight in which type of information immune-mediated inflammatory disease (IMID) patients prefer to receive after participating in

the Dutch Biologic Monitor (DBM), a PRO-based prospective cohort event monitoring system focused on adverse drug reactions (ADRs).
Methods: A survey was conducted among DBM participants that wanted information about the results. Patients' preferences were identified using twelve statements and rated with five-point Likert-type scales. Subgroup analyses and differences between statements were performed using Mann-Whitney U Tests.
Results: The survey was completed by 591 patients (response rate 67.6%). Most respondents had inflammatory rheumatic diseases (76.8%) and used adalimumab (37.2%) or etanercept (33.2%). Respondents preferred results per IMID over aggregated results (p = <0.001). Information on whether patients with similar IMIDs experience ADRs (average 4.5), which biologics are most likely to cause ADRs (4.4) and whether ADRs disappear (4.4) were most interesting.
Conclusion: DBM participants prefer to receive disease-specific information on ADRs that is tailored to their own biologic and IMID, including the outcome of ADRs.

Gepubliceerd: Expert Opin Drug Saf. 2020;19(8):1049-54.
Impact factor: 3.383; Q2

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6. EULAR/eumusc.net standards of care for rheumatoid arthritis: cross-sectional analyses of importance, level of implementation and care gaps experienced by patients and rheumatologists across 35 European countries
Meisters R, Putrik P, Ramiro S, Hifinger M, Keszei AP, van Eijk-Hustings Y, Woolf AD, Smolen JS, Stamm TA, Stoffer-Marx M, Uhlig T, Moe RH, de Wit M, Tafaj A, Mukuchyan V, Studenic P, Verschueren P, Shumnalieva R, Charalambous P, Vencovský J, Varvouni M, Kull M, Puolakka K, Gossec L, Gobejishvili N, Detert J, Sidiropoulos P, Péntek M, Kane D, Scirè CA, Arad U, Andersone D, van de Laar M, van der Helm-van Mil A, Głuszko P, Cunha-Miranda L, Berghea F, Damjanov NS, Tomšič M, Carmona L, Turesson C, Ciurea A, Shukurova S, Inanc N, Verstappen SM, Boonen A.

Objective: As part of European League against Rheumatism (EULAR)/European Musculoskeletal Conditions Surveillance and Information Network, 20 user-focused standards of care (SoCs) for rheumatoid arthritis (RA) addressing 16 domains of care were developed. This study aimed to explore gaps in implementation of these SoCs across Europe.
Methods: Two cross-sectional surveys on the importance, level of and barriers (patients only) to implementation of each SoC (0-10, 10 highest) were designed to be conducted among patients and rheumatologists in 50 European countries. Care gaps were calculated as the difference between the actual and maximum possible score for implementation (ie, 10) multiplied by the care importance score, resulting in care gaps (0-100, maximal gap). Factors associated with the problematic care gaps (ie, gap≥30 and importance≥6 and implementation<6) and strong barriers (≥6) were further analysed in multilevel logistic regression models.
Results: Overall, 26 and 31 countries provided data from 1873 patients and 1131 rheumatologists, respectively. 19 out of 20 SoCs were problematic from the perspectives of more than 20% of patients, while this was true for only 10 SoCs for rheumatologists. Rheumatologists in countries with lower gross domestic product and non-European Union countries were more likely to report problematic gaps in 15 of 20 SoCs, while virtually no differences were observed among patients. Lack of relevance

of some SoCs (71%) and limited time of professionals (66%) were the most frequent implementation barriers identified by patients.
Conclusions: Many problematic gaps were reported across several essential aspects of RA care. More efforts need to be devoted to implementation of EULAR SoCs.

Gepubliceerd: Ann Rheum Dis. 2020;79(11):1423-31.
Impact factor: 16.102; Q1

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7. A man with painful shins
Snel FW, Kootstra GJ, Vonkeman HE.

A 55-year-old man was evaluated at the outpatient rheumatology clinic with painful shins since 6 weeks. He also had a maculopapular rash on his trunk. Bone scintigraphy showed bilateral tibia periostitis. Serologic testing for syphilis was positive matching active infection. The diagnosis secondary syphilis with bilateral tibia periostitis was made.

Gepubliceerd: Ned Tijdschr Geneeskd. 2020;164.
Impact factor: nvt; nvt

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8. Two parallel short forms to measure disease- and treatment-associated knowledge in rheumatoid arthritis: application of item response theory
Spijk-de Jonge MJ, Oude Voshaar MAH, Renskers L, Huis AMP, van de Laar M, Hulscher M, van Riel P.

Objective: The aim was to develop two disease- and treatment-related knowledge about RA (DataK-RA) short forms using item response theory-based linear optimal test design.
Methods: We used the open source Excel add-in solver to program a linear optimization algorithm to develop two short forms from the DataK-RA item bank. The algorithm was instructed to optimize precision (i.e. reliability) of the scores for both short forms, subject to a number of constraints that served to ensure that each short form would include unique items and that the short forms would have similar psychometric properties. Agreement among item response theory scores obtained from the different short forms was assessed using the Bland-Altman method and Student's paired t-test. Construct validity and relative efficiency of the short forms was evaluated by relating the score to age, sex and educational attainment.
Results: Two short forms were derived from the DataK-RA item bank that satisfied all content constraints. Both short forms included 15 unique items and yielded reliable scores ($r > 0.70$), with low ceiling and floor effects. The short forms yielded statistically indistinguishable mean scores according to Student's paired t-test and Bland-Altman analysis. Scores on short forms 1 and 2 were associated with age, sex and educational attainment to a similar extent.
Conclusion: In this study, we developed two DataK-RA short forms with unique items, yet similar psychometric properties, that can be used to assess patients pre- and post-test interventions aimed at improving disease-related knowledge in RA patients.

Gepubliceerd: Rheumatol Adv Pract. 2020;4(2):rkaa012.
Impact factor: nvt; nvt

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9. Disease activity-based management of rheumatoid arthritis in Dutch daily clinical practice has improved over the past decade
Spijk-de Jonge MJ, Weijers JM, Boerboom LWM, Huis AMP, Atsma F, Van Hulst LTC, van de Laar M, Hulscher M, van Riel P.

To re-evaluate the adherence to clinical practice guidelines recommended disease activity-based management of rheumatoid arthritis (RA) in daily clinical practice, among Dutch rheumatologists in the past decade. In 2007, disease activity was measured in only 16% of outpatient visits. All rheumatologists that participated in the 2007 study were invited to re-enter our study in 2016/2017. If necessary, data were supplemented with data from other rheumatologists. For all 26 rheumatologists who agreed to participate in our study, data were collected from 30 consecutive patients that visited the outpatient clinic. Per patient, data from four consecutive rheumatologist outpatient visits were collected. Since 2007, disease activity was measured more frequently in Dutch daily clinical practice, increasing from 16 to 79% of visits (2440/3081 visits). In addition, intensification of medication based on disease activity scores increased from 33 to 50% of visits (260/525 visits). DAS/DAS28 was the most frequently used disease activity measure (1596/2440 visits). There was a wide variation among rheumatologists in measuring disease activity and intensification of medication, 20-100% and 0-75% respectively. Over the past years, there has been a large improvement in disease activity assessment in daily clinical practice. Disease activity-based medication intensifications, also called tight control or treat to target, increased to a lesser extent. Large variation between different rheumatologists and clinics indicates that there is still room for improvement. Key Points • Following guideline dissemination disease activity is assessed more frequently (79%). • There is large variation between rheumatologists, indicating room for improvement. • Finding factors that explain variation is necessary to improve tight control in daily practice.

Gepubliceerd: Clin Rheumatol. 2020;39(4):1131-9.
Impact factor: 2.394; Q3

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10. Cost-Effectiveness of a JAK1/JAK2 Inhibitor vs a Biologic Disease-Modifying Antirheumatic Drug (bDMARD) in a Treat-to-Target Strategy for Rheumatoid Arthritis
Van De Laar CJ, Oude Voshaar MAH, Fakhouri WKH, Zaremba-Pechmann L, De Leonardis F, De La Torre I, Van de Laar M.

Background: Baricitinib is a janus kinase (JAK1/JAK2) inhibitor developed for the treatment of patients suffering from rheumatoid arthritis (RA). Treating RA to the target of remission is current common practice. Cost-effectiveness of different treat-to-target (T2T) strategies, especially ones including new treatments is important for development and preference policy for treatment centers. European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) guidelines are

currently unclear about preference between a JAK1/JAK2 versus a biological disease-modifying antirheumatic drug (bDMARD).
Objective: The main goal of this paper was to evaluate the cost-effectiveness of baricitinib versus first biological for methotrexate inadequate responders in a T2T strategy using a Markov model that incorporates hospital costs as well as societal costs. Costs and utilities over five years were compared between the two strategies.
Methods: A Monte Carlo simulation model was developed to conduct cost-utility analysis from the societal perspective over 5 years. Health states were based on the DAS28-erythrocyte sedimentation rate (ESR) categories. Effectiveness of baricitinib was retrieved from randomized controlled trials. Effectiveness of all other treatments, health state utilities, medical costs, and productivity loss were retrieved from the Dutch RhEumatoid Arthritis Monitoring (DREAM) cohorts. Annual discount rates of 1.5% for utility and 4% for costs were used. Probabilistic sensitivity analysis was employed to incorporate uncertainty and assess robustness of the results.
Results: Probabilistic sensitivity analysis results showed the baricitinib strategy yielded lower costs and higher utility over a 5-year period. Scenario analyses showed the baricitinib strategy to be cost-effective in both the moderate and severe RA populations.
Conclusion: Results suggest that the use of a JAK1/JAK2 inhibitor instead of a bDMARD in a T2T approach is cost-effective in csDMARD refractory RA patients.

Gepubliceerd: Clinicoecon Outcomes Res. 2020;12:213-22.
Impact factor: nvt; nvt

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11. Patient-Reported Burden of Adverse Drug Reactions Attributed to Biologics Used for Immune-Mediated Inflammatory Diseases
van Lint JA, Jessurun NT, Hebing RCF, Hoentjen F, Tas SW, Vonkeman HE, van Doorn MBA, Sobels A, Spuls PI, van Puijenbroek EP, Nurmohamed MT, van den Bemt BJF.

Introduction: Although the burden of adverse drug reactions (ADRs) has a significant impact on patients' quality of life, thorough knowledge about patients' perspectives on the burden of ADRs attributed to biologics is lacking.
Objectives: This study was conducted to gain insight into the patient burden of ADRs experienced with biologic use.
Methods: The Dutch Biologic Monitor is a prospective, multicentre, event monitoring cohort system including information collected by web-based questionnaires from patients using biologics, mainly for immune-mediated inflammatory diseases (IMIDs). Patients were asked to complete bimonthly questionnaires on biologics used, indication for the biologic, experienced ADRs, consequences of ADRs and burden on a five-point Likert-type scale, ranging from 1 (no burden) to 5 (very high burden). We assessed potential factors associated with patient-reported burden of ADRs.
Results: A total of 1355 patients completed 6293 questionnaires between 1 January 2017 and 1 May 2019. Almost half of the patients (665 patients, 49%), 69% with rheumatic diseases and 31% with other diseases, collectively reported 1720 unique ADRs. Infections and musculoskeletal complaints were the most burdensome ADRs and injection-site reactions were the least burdensome. ADRs leading to healthcare professional contact were more burdensome than ADRs without healthcare professional contact. Smoking, respiratory and psychiatric comorbidities were

associated with higher burden of ADRs. Crohn's disease, use of adalimumab and use of sulfasalazine as combination therapy were associated with lower burden of ADRs. **Conclusions:** The patient perspective gives important insights into the burden of ADRs experienced with biologics. This information could be used by healthcare professionals to optimise treatment with biologics.

Gepubliceerd: Drug Saf. 2020;43(9):917-25.
Impact factor: 3.442; Q1

Totale impact factor: 36.703
Gemiddelde impact factor: 3.337

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 5.605
Gemiddelde impact factor: 1.401

Raad van Bestuur

1. Delirium, functional decline and quality of life after transcatheter aortic valve implantation: An explorative study
Beishuizen SJ, Festen S, Loonstra YE, van der Werf HW, de Rooij SE, van Munster BC.

Aim: Transcatheter aortic valve implantation (TAVI) has become an important treatment option for older patients with severe aortic stenosis. However, not all patients benefit from this procedure in terms of functional outcome and quality of life. This complicates patient selection and shared decision-making. Postoperative delirium might negatively affect patient outcomes after TAVI. We therefore studied the potential relationship between postoperative delirium and functional outcome, and how this impacts quality of life after TAVI.
Methods: This was a prospective cohort study of 91 consecutive patients undergoing TAVI between 2015 and 2017 at an academic medical center. All patients underwent a Comprehensive Geriatric Assessment before TAVI. Delirium symptoms were assessed daily during hospitalization. Follow up was carried out between 6 and 12 months postprocedure. The primary outcome was functional decline or death at follow up. Secondarily, we measured quality of life at follow up.
Results: The incidence of postoperative delirium was 15.4%. In total, 38.5% of patients experienced functional decline, and 11.0% died during a median follow-up period of 7 months. Delirium resulted in a fourfold increased odds of the combined outcome of functional decline or death. Quality of life was lower in patients that experienced this outcome.
Conclusion: In a cohort of TAVI patients, functional decline or death was a frequent outcome in the first year postprocedure. Postoperative delirium increased the odds for this outcome substantially. This suggests that delirium risk should be an important factor to consider in shared decision-making for TAVI patients. Geriatr Gerontol Int 2020; 20: 1202-1207.

Gepubliceerd: Geriatr Gerontol Int. 2020;20(12):1202-7.
Impact factor: 2.022; Q2

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2. The influence of a serious game's narrative on students' attitudes and learning experiences regarding delirium: an interview study
Buijs-Spanjers KR, Harmsen A, Hegge HH, Spook JE, de Rooij SE, Jaarsma D.

Background: Delirium is a neuropsychiatric syndrome that affects patients' attention and awareness as a result of a physical condition. In recent years, persistent gaps in delirium education have led to suboptimal delirium care. Still, little is known about what are the most important aspects of effective delirium education. Serious games are both entertainment and an interactive, safe learning environment where players can experiment and create new knowledge. They have the potential to contribute to improved delirium education. We used a video-based serious games' narrative to explore aspects essential to enhance students' attitudes and learning experiences regarding delirium.

Methods: We created a semi-structured interview guide and interviewed seven nursing and nine medical students about their attitudes and learning experiences, after they had played the game. A qualitative descriptive design and inductive content analysis with constant comparison were used.
Results: The patient's and nurse's perspective, interactivity to experiment, realistic views on care options, and feedback on care actions were important for enhancing students' attitudes and learning experiences regarding delirium. Students felt these aspects encouraged them to get actively involved in and experiment with the study material, which in turn led to enhanced reflection on delirium care and education. Our findings highlight the importance of a more patient-oriented focus to delirium education to drive attitudinal change. Students' learning experiences were further enhanced through their affective responses provoked by the perspectives, interactivity, realism, and feedback.
Conclusions: Students considered the characters' perspectives, interactivity, realism, and feedback important aspects of the game to enhance their attitudes towards delirious patients and enrich their learning experiences. A patient-oriented narrative provides a clinically relevant experience in which reflection plays an important role. The serious game also serves as medium to actively experiment with care solutions to create better understanding of how healthcare professionals can influence a delirious patient's experience.

Gepubliceerd: BMC Med Educ. 2020;20(1):289.
Impact factor: 1.831; Q2

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3. Reasons to Engage in and Learning Experiences From Different Play Strategies in a Web-Based Serious Game on Delirium for Medical Students: Mixed Methods Design
Buijs-Spanjers KR, Hegge HH, Cnossen F, Jaarsma DA, de Rooij SE.

Background: Although many studies have recently been published on the value of serious games for medical education, little attention has been given to the role of dark play (choosing unacceptable actions in games).
Objective: This study aimed to investigate potential differences in the characteristics of medical students who have the opportunity to choose normal or dark play in a serious game. This study also aimed to compare their reasons for choosing a play strategy and their perceptions of what they learned from their game play.
Methods: We asked undergraduate medical students to play a serious game in which they had to take care of a patient with delirium (The Delirium Experience). After getting acquainted with the game, students could opt for normal or dark play. Student characteristics (age, gender, experience with caring for older or delirious patients, and number of completed clerkships) were collected, and the Delirium Attitude Scale and Learning Motivation and Engagement Questionnaire were administered. Reasons for choosing normal or dark play were evaluated with an open-ended question. Information on lessons they had learned from the game was collected using an open-ended question and self-reported knowledge on delirium.
Results: This study had 160 participants (89 normal play, 71 dark play). Male students (26/160, 56.5%) chose dark play significantly more often than female students (45/160, 39.5%; P=.049). We did not find significant differences in student characteristics or measurement outcomes between play strategies. Participants' main

reason for choosing normal play was to learn how to provide care to delirious patients, and the main reason for dark play was to gain insight into what a delirious patient has to endure during delirious episodes. All participants learned what to do when taking care of a delirious patient and gained insight into how a patient experiences delirium. We found no differences in self-reported knowledge.
Conclusions: When medical students have the opportunity to choose dark play in a serious game, half of them will probably choose this play strategy. Male students will more likely opt for dark play than female students. Choice of play strategy is not affected by any other student characteristic or measurement outcome. All students learned the same lessons from playing the game, irrespective of their learning strategy.

Gepubliceerd: JMIR Serious Games. 2020;8(3):e18479.
Impact factor: 3.526; Q2

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4. Clinical impression for identification of vulnerable older patients in the emergency department
Calf AH, Lubbers S, van den Berg AA, van den Berg E, Jansen CJ, van Munster BC, de Rooij SE, Ter Maaten JC.

Objectives: To investigate whether the clinical impression of vulnerability and the Dutch Safety Management Program (VMS), a screening instrument on four geriatric domains (activities in daily living, falls, malnutrition, delirium) are useful predictors of 1-year mortality in older patients in the emergency department.
Methods: This was a prospective observational study in the emergency department of a tertiary care teaching hospital. Patients aged 65 years and older visiting the emergency department, and their attending physicians and nurses were included. Clinical impression of vulnerability appraised by physician and nurse and the VMS-screening were recorded.
Results: We included 196 patients of whom 64.8%, 61.7%, and 52.6% were considered vulnerable based on the clinical impression of vulnerability of physicians, nurses, and VMS-screening, respectively. Agreement between clinical impression of vulnerability of physicians and nurses, and VMS-screening were both fair (overall agreement 63.3% for both, and respectively kappa 0.32 and kappa 0.31). Clinical impression of vulnerability of physicians, nurses, and VMS-screening had a sensitivity of respectively 94%, 86%, and 73% for predicting 1-year mortality. A positive clinical impression of vulnerability was associated mostly with factors which can be observed directly during first patient contact after arrival to the emergency department, such as age, nutritional status, and functional impairment.
Conclusion: The clinical impression of vulnerability is a simple dichotomous question which can be used as a first step in the identification of vulnerable older emergency department patients, whereas the more time-consuming VMS-screening is more specific for detection of vulnerability. The clinical impression of vulnerability is therefore useful in a busy emergency department environment where time and resources are limited.

Gepubliceerd: Eur J Emerg Med. 2020;27(2):137-41.
Impact factor: 2.170; Q2

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5. Physical and Pharmacological Restraints in Hospital Care: Protocol for a Systematic Review
de Bruijn W, Daams JG, van Hunnik FJG, Arends AJ, Boelens AM, Bosnak EM, Meerveld J, Roelands B, van Munster BC, Verwey B, Figee M, de Rooij SE, Mocking RJT.

Background: Physical and pharmacological restraints, defined as all measures limiting a person in his or her freedom, are extensively used to handle unsafe or problematic behavior in hospital care. There are increasing concerns as to the extent with which these restraints are being used in hospitals, and whether their benefits outweigh their potential harm. There is currently no comprehensive literature overview on the beneficial and/or adverse effects of the use of physical and pharmacological restraints in the hospital setting.
Methods: A systematic review of the existing literature will be performed on the beneficial and/or adverse effects of physical and pharmacological restraints in the hospital setting. Relevant databases will be systematically searched. A dedicated search strategy was composed. A visualization of similarities (VOS) analysis was used to further specify the search. Observational studies, and if available, randomized controlled trials reporting on beneficial and/or adverse effects of physical and/or pharmacological restraints in the general hospital setting will be included. Data from included articles will be extracted and analyzed. If the data is suitable for quantitative analysis, meta-analysis will be applied.
Discussion: This review will provide data on the beneficial and/or adverse effects of the use of physical and pharmacological restraints in hospital care. With this review we aim to guide health professionals by providing a critique of the available evidence regarding their choice to either apply or withhold from using restraints. A limitation of the current review will be that we will not specifically address ethical aspects of restraint use. Nevertheless, the outcomes of our systematic review can be used in the composition of a multidisciplinary guideline. Furthermore, our systematic review might determine knowledge gaps in the evidence, and recommendations on how to target these gaps with future research.
Systematic Review Registration: PROSPERO registration number: CRD42019116186.

Gepubliceerd: Front Psychiatry. 2020;10:921.
Impact factor: 2.849; Q2

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6. Translation and validation of the Dutch Pittsburgh Fatigability Scale for older adults
Feenstra M, Smidt N, van Munster BC, Glynn NW, de Rooij SE.

Background: The original Pittsburgh Fatigability Scale (PFS) was developed to assess perceived fatigability in older adults. The objective of this study was to translate the PFS into Dutch and investigate its validity and reliability among hospitalized older adults aged ≥70 years.
Methods: The PFS was translated into Dutch and pretested for comprehensibility by the Three-Step Test Interview method. The factor structure underlying the final version was evaluated by confirmatory factor analysis (CFA) and exploratory factor

analyses (EFA). Internal consistency of the identified subscales was evaluated by Cronbach's alpha. Construct validity was evaluated by hypothesis testing. Test-retest reliability was evaluated using intraclass correlation coefficients (ICC) and Bland Altman plots.
Results: The validation sample included 233 patients. CFA of the original factor structure resulted in poor model fit in our Dutch sample. EFA of PFS physical and mental subscales resulted in a two-factor solution underlying the data with good internal consistency of the identified subscales (Cronbach's alpha: 0.80-0.92). Five out of six hypotheses were confirmed, indicating good construct validity. Retest assessments were performed among 50 patients and showed good reliability for both the physical (ICC: 0.80, 95%CI: 0.68; 0.88) and mental subscale (ICC: 0.81, 95%CI: 0.68; 0.89).
Conclusion: The Dutch PFS is a valid and reliable instrument to assess fatigability in older hospitalized patients.

Gepubliceerd: BMC Geriatr. 2020;20(1):234.
Impact factor: 3.077; Q2

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7. Trajectories of self-rated health in an older general population and their determinants: the Lifelines Cohort Study
Feenstra M, van Munster BC, MacNeil Vroomen JL, de Rooij SE, Smidt N.

Objectives: Poor self-rated health (SRH) is a strong predictor of premature mortality in older adults. Trajectories of poor SRH are associated with multimorbidity and unhealthy behaviours. Whether trajectories of SRH are associated with deviating physiological markers is unclear. This study identified trajectories of SRH and investigated the associations of trajectory membership with chronic diseases, health risk behaviours and physiological markers in community-dwelling older adults.
Study Design and Setting: Prospective general population cohort.
Participants: Trajectories of SRH over 5 years were identified using data of 11 600 participants aged 65 years and older of the Lifelines Cohort Study.
Outcome Measures: Trajectories of SRH were the main outcome. Covariates included demographics (age, gender, education), chronic diseases, health-risk behaviour (physical activity, smoking, drinking) and physiological markers (body mass index, cardiovascular function, lung function, glucose metabolism, haematological condition, endocrine function, renal function, liver function and cognitive function).
Results: Four stable trajectories were identified, including excellent (n=607, 6%), good (n=2111, 19%), moderate (n=7677, 65%) and poor SRH (n=1205, 10%). Being women (OR: 1.4; 95% CI: 1.0 to 1.9), low education (OR: 2.1; 95% CI: 1.5 to 3.0), one (OR: 10.4; 95% CI: 7.4 to 14.7) or multiple chronic diseases (OR: 37.8; 95% CI: 22.4 to 71.8), smoking (OR: 1.8; 95% CI: 1.0 to 3.2), physical inactivity (OR: 3.1; 95% CI: 1.8 to 5.2), alcohol abstinence (OR: 2.2; 95% CI: 1.4 to 3.2) and deviating physiological markers (OR: 1.5; 95% CI: 1.1 to 2.0) increase the odds for a higher probability of poor SRH trajectory membership compared with excellent SRH trajectory membership.
Conclusion: SRH of community-dwelling older adults is stable over time with the majority (65%) having moderate SRH. Older adults with higher probabilities of poor SRH often have unfavourable health status.

Gepubliceerd: BMJ Open. 2020;10(2):e035012.
Impact factor: 2.496; Q2

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8. COVID-19: Technology-Supported Remote Assessment of Pediatric Asthma at Home
van der Kamp MR, Tabak M, de Rooij S, van Lierop PPE, Thio BJ.

The COVID-19 crisis has pressured hospital-based care for children with high-risk asthma as they have become deprived of regular clinical evaluations. However, COVID-19 also provided important lessons about implementing novel directions for care. Personalized eHealth technology, tailored to the individual and the healthcare system, could substitute elements of hospital care and facilitate early and appropriate medical anticipation in response to imminent loss of control. This perspective article discusses new approaches to the clinical, organizational, and scientific aspects of the use of eHealth technology in pediatric asthma care in times of COVID-19, as illustrated by a case report of an acute asthma exacerbation possibly caused by COVID-19 infection.

Gepubliceerd: Front Pediatr. 2020;8:529.
Impact factor: 2.634; Q1

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9. Development of a new tool for the assessment of patient-defined benefit in hospitalised older patients: the Patient Benefit Assessment Scale for Hospitalised Older Patients (P-BAS HOP)
van der Kluit MJ, Dijkstra GJ, van Munster BC, De Rooij S.

Objectives: To support the shift from disease-oriented towards goal-oriented care, we aimed to develop a tool which is capable both to identify priorities of an individual older hospitalised patient and to measure the outcomes relevant to him.
Design: Mixed-methods design with open interviews, three step test interviews (TSTIs) and a quantitative field test.
Setting: University teaching hospital and a regional teaching hospital.
PARTICIPANTS: Hospitalised patients ages 70 years and older.
Results: The Patient Benefit Assessment Scale for Hospitalised Older Patients (P-BAS HOP) consists of a baseline questionnaire and an evaluation questionnaire. Items were based on 15 qualitative interviews with hospitalised older patients. Feedback from a panel of four community-dwelling older persons resulted in some adaptations to wording and one additional item. Twenty-six hospitalised older patients participated in TSTIs with Version 1 of the baseline questionnaire, revealing indications for a good content validity and barriers in completion behaviour, global understanding and understanding of individual items, which were solved with several adaptations. Four additions were made by participants. After TSTIs with ten patients with the evaluation questionnaire, one adaptation was made. A field test with 91 hospitalised older patients revealed a small number of missing values.To enhance the feasibility, the number of items was reduced from 32 to 22, based on correlations and mean impact score. The field test was repeated with 104 other patients in a regional teaching hospital. To enhance the understanding, the tool was split into two phases. This version was tested with TSTIs with eight patients and appeared to be

understandable. The final version was an interview-based tool and took about 11 min to complete.
Conclusions: The P-BAS HOP is a potentially suitable tool to identify priorities and relevant outcomes of the individual patient. Further research is needed to investigate its validity, reliability and responsiveness.

Gepubliceerd: BMJ Open. 2020;10(11):e038203.
Impact factor: 2.496; Q2

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10. Uptake and effectiveness of a tailor-made online lifestyle programme targeting modifiable risk factors for dementia among middle-aged descendants of people with recently diagnosed dementia: study protocol of a cluster randomised controlled trial (Demin study)
Vrijsen J, Abu-Hanna A, Maeckelberghe EL, De Deyn PP, de Winter AF, Reesink FE, Oude Voshaar RC, Buskens E, de Rooij SE, Smidt N.

Introduction: Descendants of patients with dementia have a higher risk to develop dementia. This study aims to investigate the uptake and effectiveness of an online tailor-made lifestyle programme for dementia risk reduction (DRR) among middle-aged descendants of people with recently diagnosed late-onset dementia.
Methods and Analysis: Demin is a cluster randomised controlled trial, aiming to include 21 memory clinics of which 13 will be randomly allocated to the passive (poster and flyer in a waiting room) and 8 to the active recruitment strategy (additional personal invitation by members of the team of the memory clinic). We aim to recruit 378 participants (40-60 years) with a parent who is recently diagnosed with Alzheimer's disease or vascular dementia at one of the participating memory clinics. All participants receive a dementia risk assessment (online questionnaire, physical examination and blood sample) and subsequently an online tailor-made lifestyle advice regarding protective (Mediterranean diet, low/moderate alcohol consumption and high cognitive activity) and risk factors (physical inactivity, smoking, loneliness, cardiovascular diseases (CVD), hypertension, high cholesterol, diabetes, obesity, renal dysfunction and depression) for dementia. The primary outcome is the difference in uptake between the two recruitment strategies. Secondary outcomes are change(s) in (1) the Lifestyle for Brain Health score, (2) individual health behaviours, (3) health beliefs and attitudes towards DRR and (4) compliance to the tailor-made lifestyle advice. Outcomes will be measured at 3, 6, 9 and 12 months after baseline. The effectiveness of this online tailor-made lifestyle programme will be evaluated by comparing Demin participants to a matched control group (lifelines cohort).
Ethics and Dissemination: This study has been approved by the Dutch Ministry of Health, Welfare and Sport according to the Population Screening Act. All participants have to give online informed consent using SMS-tan (transaction authentication number delivered via text message). Findings will be disseminated through peer-reviewed journals and (inter)national conferences.
Trial registration number: NTR7434.

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Impact factor: 2.496; Q2

Totale impact factor: 25.597
Gemiddelde impact factor: 2.560

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 5.169
Gemiddelde impact factor: 1.292

Thoraxchirurgie

1. Infective endocarditis in the Netherlands: current epidemiological profile and mortality : An analysis based on partial ESC EORP collected data
El Kadi S, van den Buijs DMF, Meijers T, Gilbers MD, Bekkers S, van Melle JP, Riezebos RK, Blok WL, Tanis W, Wahadat AR, Roos-Hesselink JW, van der Spoel TIG, Chamuleau SAJ, Kamp O.

Introduction: Infective endocarditis (IE) is associated with a high in-hospital and long term mortality. Although progress has been made in diagnostic approach and management of IE, morbidity and mortality of IE remain high. In the latest European guidelines, the importance of the multi-modality imaging in diagnosis and follow up of IE is emphasized. AIM: The aim was to provide information regarding mortality and adverse events of IE, to determine IE characteristics and to assess current use of imaging in the diagnostic workup of IE.
Methods: This is a prospective observational cohort study. We used data from the EURO-ENDO registry. Seven hospitals in the Netherlands have participated and included patients with IE between April 2016 and April 2018.
Results: A total of 139 IE patients were included. Prosthetic valve endocarditis constituted 32.4% of the cases, cardiac device related IE 7.2% and aortic root prosthesis IE 3.6%. In-hospital mortality was 14.4% (20 patients) and one-year mortality was 21.6% (30 patients). The incidence of embolic events under treatment was 16.5%, while congestive heart failure or cardiogenic shock occurred in 15.1% of the patients. Transthoracic and transoesophageal echocardiography were performed most frequently (97.8%; 81.3%) and within 3 days after IE suspicion, followed by (18)F-fluorodeoxyglucose positron emission tomography/computed tomography (45.3%) within 6 days and multi-slice computed tomography (42.4%) within 7 days.
Conclusion: We observed a high percentage of prosthetic valve endocarditis, rapid and extensive use of imaging and a relatively low in-hospital and one-year mortality of IE in the Netherlands. Limitations include possible selection bias.

Gepubliceerd: Neth Heart J. 2020;28(10):526-36.
Impact factor: 1.933; Q3

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2. High incidence of (ultra)low oesophageal temperatures during cryoballoon pulmonary vein isolation for atrial fibrillation
Molenaar MMD, Hesselink T, Scholten MF, Kraaier K, Bouman DE, Brusse-Keizer M, Stevenhagen YJ, van Dessel P, Ten Haken B, Grandjean JG, van Opstal JM.

Background: Low oesophageal temperatures (OTs) during cryoballoon pulmonary vein isolation (PVI) have been associated with complications. This study assessed the incidence of low OT in clinical practice during cryoballoon PVI and verified possible predictive values for low OT.
Methods: Consecutive patients who underwent PVI using the second-generation cryoballoon were retrospectively included. The distance from the oesophagus to the different pulmonary veins (PVs) (OP distance), body mass index (BMI), sex, age, balloon temperature and application time were studied as potential predictors of low OTs. Computed tomography was performed before the procedure to determine the

OP distance. OT was measured using an oesophageal temperature probe. Applications were ended prematurely if the OT reached <16 °C. Low and ultralow OT were defined as OT <20 and <16 °C respectively.
Results: Two hundred and four patients were included. Low OT was observed in 54 patients (26%) and 27 patients (13%) reached ultralow OTs. OP distance was the only predictor of low OTs after multivariate analysis. A cut-off value of 19 mm showed 96.2% sensitivity and 37.8% specificity in predicting low OTs. No clinically relevant relation was found between low OTs and BMI, age, sex, balloon temperature or application duration.
Conclusions: The incidence of low OT was 26% for cryoballoon PVI. OP distance was the only predictor of low OTs. Since an OP distance <19 mm was present in all patients in at least one PV, we recommend routine OT measurement during PVI cryoballoon therapy to prevent oesophagus-related complications.

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Impact factor: 1.933; Q3

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3. Shorter RSPV cryoapplications result in less phrenic nerve injury and similar 1-year freedom from atrial fibrillation
Molenaar MMD, Hesselink T, Ter Bekke RMA, Scholten MF, Manusama R, Pison L, Brusse-Keizer M, Kraaier K, Ten Haken B, Grandjean JG, Timmermans CC, van Opstal JM.

Background: In the 123-study, we prospectively assessed, in a randomized fashion, the minimal cryoballoon application time necessary to achieve pulmonary vein (PV) isolation (PVI) in patients with paroxysmal atrial fibrillation (AF) with the aim to reduce complications by shortening the application duration. The first results of this study demonstrated that shortened cryoballoon applications (<2 minutes) resulted in less phrenic nerve injury (PNI) without compromising acute isolation efficacy for the right PVs. We now report the 1-year follow-up results regarding safety and efficacy of shorter cryoballoon applications.
Methods: A total of 222 patients with AF were randomized to two applications of 1 min "short," 2 min "medium," or 3 min "long" duration, 74 per group. Recurrence of AF and PV reconduction at 1-year follow-up were assessed.
Results: The overall 1-year freedom from AF was 79% and did not differ significantly between the short, medium, and long application groups (77%, 74%, and 85% for short, medium, and long application groups, respectively; P = 0.07). In 30 patients, a redo PVI procedure was performed. For all four PVs, there was no significant difference in reconduction between the three groups. Reconduction was most common in the left superior PV (57%). The right superior PV (RSPV) showed significantly less reconduction (17%) compared to the other PVs.
Conclusions: Shortening cryoballoon applications of the RSPV to <2 minutes results in less PNI, while acute success and 1-year freedom from AF are not compromised. Therefore, shorter cryoballoon applications (especially) in the RSPV could be used to reduce PNI.

Gepubliceerd: Pacing Clin Electrophysiol. 2020;43(10):1173-9.
Impact factor: 1.303; Q4

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4. Organization of outcome-based quality improvement in Dutch heart centres
van Veghel D, Daeter EJ, Bax M, Amoroso G, Blaauw Y, Camaro C, Cummins P, Halfwerk FR, Wijdh-den Hamer IJ, de Jong J, Stooker W, van der Wees PJ, van der Nat PB.

Aims: Fourteen Dutch heart centres collected patient-relevant outcomes to support quality improvements in a value-based healthcare initiative that began in 2012. This study aimed to evaluate the current state of outcome-based quality improvement within six of these Dutch heart centres.
Methods and Results: Interviews and questionnaires among physicians and healthcare professionals in the heart centres were combined in a mixed-methods approach. The analysis indicates that the predominant focus of the heart centres is on the actual monitoring of outcomes. A systematic approach for the identification of improvement potential and the selection and implementation of improvement initiatives is lacking. The organizational context for outcome-based quality improvement is similar in the six heart centres.
Conclusion: Although these heart centres in the Netherlands measure health outcomes for the majority of cardiac diseases, the actual use of these outcomes to improve quality of care remains limited. The main barriers are limitations regarding (i) data infrastructure, (ii) a systematic approach for the identification of improvement potential and the selection and implementation of improvement initiatives, (iii) governance in which roles and responsibilities of physicians regarding outcome improvement are formalized, and (iv) implementation of outcomes within hospital strategy, policy documents, and the planning and control cycle.

Gepubliceerd: Eur Heart J Qual Care Clin Outcomes. 2020;6(1):49-54.
Impact factor: nvt; nvt

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5. Implementation of a specific safety check is associated with lower postoperative mortality in cardiac surgery
Spanjersberg AJ, Ottervanger JP, Nierich AP, Speekenbrink RGH, Stooker W, Hoogendoorn M, van Veghel D, Houterman S, Brandon Bravo Bruinsma GJ.

Introduction: In cardiac surgery, a preincision safety checklist may decrease complications and improve survival. Until now, it has not been demonstrated whether the implementation of such a checklist indeed reduces mortality.
Objective: Introduction of a preincision safety checklist on mortality was studied in a large adult cardiac surgery population.
Methods: This prospective, multicenter cohort study included 5937 consecutive adult patients, undergoing cardiac surgery, between January 2015 and December 2015, in 7 Dutch non-academic cardiac centers. The Isala Safety Check (ISC) is a short checklist addressing specific cardiac surgery safety items, in combination with a concise postinduction transesophageal echocardiography, which was gradually over time introduced in the 7 hospitals during 2015. We compared 120-day mortality and major complications between patients undergoing surgery with or without the use of the ISC. Propensity matching and Cox regression analyses were performed to adjust for potential confounders.

Results: The ISC was applied in 2718 patients (46%). Comorbidity and age were comparable in both groups. In the ISC group, 120-day mortality was significantly lower (1.7% vs 3.0%; P < .01). Both after propensity matching (hazard ratio, 0.44; 95% confidence interval, 0.22-0.87) and Cox regression analysis (hazard ratio, 0.56; 95% confidence interval, 0.35-0.90), the use of the ISC was still associated with reduced 120-day mortality. Deep sternal wound infection, surgical re-exploration, and stroke were not significantly different between both groups.
Conclusions: Application of a short preincision safety checklist in a mixed population of adult cardiac surgery patients is associated with significantly reduced 120-day mortality.
Keywords: patient safety; safety checklist; adult cardiac surgery; mortality; best practice; outcome

Gepubliceerd: J Thorac Cardiovasc Surg 2020;159(5):1882-90
Impact factor: 4.451; Q1

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6. Thoracotomy Versus Sternotomy for Patent Ductus Arteriosus Closure in Preterm Neonates,
Verhaegh AJFP, Accord RE, Kooi EMW, Arrigoni SC, Bos AF, Berger RMF, Ebels T,

Background: To date, a posterolateral thoracotomy approach is considered the gold standard for surgical closure of patent ductus arteriosus (PDA), also in preterm neonates. However, a posterolateral thoracotomy approach can induce post-thoracotomy lung injury of the immature and vulnerable lungs of preterm neonates. Therefore, this study aims to compare a posterolateral thoracotomy and median sternotomy for surgical closure of PDA in preterm neonates.
Methods: Between September 2010 and November 2014, both surgical approaches were used to treat a symptomatic PDA in very and extremely preterm neonates. The hospital records of all these neonates were retrospectively reviewed to assess all-cause mortality and postoperative morbidity in both groups.
Results: Despite comparable preoperative patient profiles, the postoperative pulmonary complication rate was significantly lower in the median sternotomy group (52.9% vs 94.7%; P = .006). Moreover, significantly lower mean airway pressures (MAPs) were seen in the median sternotomy group directly after surgery (ΔMAP median [interquartile range], 0.00 [2.13] vs 0.80 [1.67] cmH2O; P = .025). Postoperative blood transfusion (median [interquartile range], 20 [14] vs 17 [16] mL; P = .661) rates did not differ between both approaches. In addition, Kaplan-Meier survival analysis demonstrated no statistically significant differences between both groups.
Conclusions: In our experience, a median sternotomy approach for surgical PDA closure is at least noninferior to a posterolateral thoracotomy approach. Given the lower postoperative pulmonary complication rate and lower postoperative MAPs directly after surgery, the median sternotomy approach may be considered superior for preterm neonates with immature and vulnerable lungs.

Gepubliceerd: Ann Thorac Surg 2020;109(1):171-7
Impact factor: 3.639; Q1

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7. Thoracoscopic sympathicotomy for the treatment of intolerable palmar and axillary hyperhidrosis in children is associated with high recurrence rates
Verhaegh AJFP, Kuijpers M, Boon M, de Jongste MJL, Bouma W, Mariani MA, Klinkenberg TJ.

Background: Treatment of palmar and axillary primary focal hyperhidrosis (PFH) in children up to 16 years using thoracoscopic sympathicotomy is supported by scarce evidence. Therefore, this study aimed to summarize the results of our standardized bilateral, one-stage, single-port sympathicotomy (BOSS) in children up to 16 years of age.
Methods: Consecutive children (n = 14) up to 16 years of age undergoing BOSS between October 2011 and June 2015 in our institution were included in this retrospective study.
Results: Recurrence of primary hyperhidrosis was noted in seven patients (50.0%), of whom five patients (35.7%) underwent reoperation. Reoperations were associated with placement of additional thoracoscopic ports (n = 1; 12.5%), intraoperative placement of pleural drains (n = 2; 25%), and prolonged air leak (n = 1; 12.5%). Despite the high recurrence and reoperation rates, overall patient satisfaction was high with a median satisfaction score of 7.5 (interquartile range of 1.75; range: 4-9).
Conclusion: Although the overall patient satisfaction score in our cohort was good, BOSS for the treatment of intolerable palmar and axillary PFH in children up to 16 years of age is associated with a high recurrence and reoperation rate.

Gepubliceerd: Pediatr Dermatol 2020;37:987-92
Impact factor: 1.164; Q4

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8. Thoracoscopic sympathicotomy in children for the treatment of palmar and axillary primary focal hyperhidrosis: Caution advocated,
Verhaegh AJFP, Kuijpers M, Klinkenberg TJ,

Gepubliceerd: J Pediatr Surg 2020;55(12):2847-8
Impact factor: 1.919; Q2

Totale impact factor: 16.342
Gemiddelde impact factor: 2.043

Aantal artikelen 1e, 2e of laatste auteur: 6
Totale impact factor: 11.891
Gemiddelde impact factor: 1.982