Wetenschappelijk onderzoek in Medisch Spectrum Twente

2015

Inhoudsopgave

Voorwoord

Voor u ligt de zevende editie van het jaarlijkse overzicht van het wetenschappelijk overzicht wat door medewerkers van Medisch Spectrum Twente in 2015 is gepubliceerd. 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 2015 zijn. De zogenaamde “Epub Ahead of Print” artikelen komen in de volgende uitgave. Daarnaast worden ook peer-reviewed artikelen uit Nederlandstalige tijdschriften opgenomen.

In 2015 zijn 245 unieke publicaties verschenen in peer-reviewed tijdschriften. Dit is flink meer dan alle voorgaande jaren! De gemiddelde impact score van alle artikelen is 5.062, wat nagenoeg vergelijkbaar is met ons topjaar tot op heden: 2010. Dit jaar hebben we ook goed gescoord in de toptijdschriften: éénmaal in de New England Journal of Medicine en vijf artikelen in de Lancet.

Qua promoties was 2015 na het topjaar 2014 een iets minder goed jaar met 7 promoties in MST. Nog steeds niet slecht natuurlijk.

Inmiddels wordt ook in STZ-verband een lijst van publicaties door de STZ ziekenhuizen bijgehouden. Daarin worden alleen publicaties opgenomen waarin “Medisch Spectrum Twente” als affiliatie gemeld staat. Ik doe bij dezen dan ook de oproep aan iedereen om **bij elke publicatie Medisch Spectrum Twente te vermelden als affiliatie**, ook als je hier maar deeltijd werkt en het onderzoek misschien grotendeels elders is uitgevoerd. Iedereen met een contract in MST hoort bij 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 1^{e}, 2^{e} of laatste auteur is.

Om de ontwikkeling te kunnen volgen zijn de ranglijsten van 2015 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

	2009	2010	2011	2012	2013	2014	2015
Aantal unieke publicaties	109	177	190	213	191	212	245
Gemiddelde impact factor	3,16	5,12	3,63	3,97	4,38	4,03	5,06

Top 3: Aantal publicaties:

2012			2013			2014			2015		
1	Cardiologie	33	1	Neurologie	34	1	Neurologie	39	1	Medical School	35
2	Medical School	27	2	Reumatologie	32	2	Medical School	33	2	Neurologie	33
3	Heelkunde	24	3	Medical School	24	3	Cardiologie	25	3	Heelkunde	31

Top 3: Totale impact factor score:

1	Cardiologie	148	1	Neurologie	276	1	Cardiologie	149	1	Neurologie	184
2	Interne	107	2	Reumatologie	157	2	Neurologie	110	2	Heelkunde	178
3	Intensive Care	80	3	Cardiologie	106	3	Reumatologie	107	3	Cardiologie	141

Top 3: Gemiddelde impact factor score:

1	Anesthesie	30	1	Neurochirurgie	24	1	MDL	6.1	1	Gynaecologie	12.5
2	Interne	7	2	Klin. Chemie	10	2	Pathologie	6.0	2	MDL	11.8
3	Radiotherapie	6	3	Neurologie	8	3	Cardiologie	6.0	3	Klin. chemie	10.5

Top 3: Aantal publicaties als 1e, 2e of laatste auteur:

1	Cardiologie	21	1	Reumatologie	24	1	Neurologie	22	1	Neurologie	17
2	Reumatologie	18	2	Neurologie	19	2	Medical School	18	2	Medical School	16
3	MDL	12	3	Cardiologie	16	3	Cardiologie	15	3	Cardiologie	15
							Reumatologie	15		Heelkunde	15

Top 3: Totale impact factor score als 1e, 2e of laatste auteur:

1	Cardiologie	126	1	Reumatologie	83	1	Cardiologie	98	1	Cardiologie	65
2	Reumatologie	55	2	Neurologie	66	2	Neurologie	52	2	Neurologie	48
3	Neurologie	43	3	Cardiologie	55	3	Medical School	51	3	Reumatologie	46

Top 3: Gemiddelde impact factor score als 1e, 2e of laatste auteur:

1	Interne	6	1	Kindergnkd	5	1	Cardiologie	6.5	1	Gynaecologie	6.0
2	Cardiologie	6	2	Radiotherapie	5	2	Intensive Care	6.1	2	Pathologie	5.6
3	Intensive Care	5	3	Microbiologie	5	3	MDL	4.7	3	Intensive Care	5.4

Overzicht aantal publicaties per vakgroep:

	2009	2010	2011	2012	2013	2014	2015
Anesthesiologie	1	2	1	1	0	0	2
Automatisering	0	0	0	0	0	0	1
Cardiologie	14	14	23	33	21	25	28
Gynaecologie	2	15	7	5	5	7	6
Heelkunde	16	38	26	24	13	21	31
Intensive Care	1	2	12	16	11	13	14
Interne Geneeskunde	12	13	17	15	16	20	17
Kindergeneeskunde	5	4	7	6	5	3	11
Klinische Chemie	4	14	10	6	2	6	7
Klinische Farmacie	4	3	4	4	4	6	8
Medische Techniek	0	1	0	0	0	0	2
Klinische Psychologie	0	0	1	4	3	4	1
KNO	0	1	1	0	0	1	1
Laboratorium voor Microbiologie	4	6	8	5	7	2	2
Longziekten	8	5	17	10	11	12	16
MDL	4	5	4	13	6	11	5
Medical School Twente	12	13	13	27	24	33	35
Mond- kaak-, aangezichtschirurgie	0	1	0	1	3	0	0
Neurochirurgie	3	0	0	2	1	5	9
Neurologie	11	23	21	19	34	39	33
Nucleaire Geneeskunde	1	1	0	1	0	0	2
Orthopedie	1	2	3	3	0	4	7
Pathologie	1	6	9	12	1	5	8
Plastische Chirurgie	4	1	1	0	2	0	2
Psychiatrie	1	0	0	0	0	0	1
Radiologie	2	11	6	7	6	11	14
Radiotherapie	2	4	5	10	3	5	12
Reumatologie	14	17	25	21	32	20	23
Revalidatiegeneeskunde	2	5	4	11	7	8	6
Spoedeisende Hulp	0	2	1	0	0	0	0
Tandheelkunde	0	0	1	0	0	0	0
Thoraxchirurgie	4	2	5	3	4	3	2

Promoties in MST in 2015
Cardiologie

Lesion Morphology, Vessel Anatomy and the Outcome of Coronary Stenting

Insight from the Twente Trials

Academisch Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Twente
op gezag van de Rector Magnificus
prof. dr. E. Brinksma
ten overstaan van een door het college voor promoties ingestelde
commissie, in het openbaar te verdedigen in de Agnietenkapel
op woensdag 17 juni 2015, te 16:45 uur

door

Ming Kai Lam

geboren op 1 oktober 1984 te Emmen

Promotor:	Prof. dr. C. von Birgelen, University of Twente, Enschede Prof. dr. M.J. Ijzerman, University of Twente, Enschede
Copromotores:	Dr. C.J.M. Doggen, University of Twente, Enschede
Overige leden:	Prof. dr. J. van der Palen, University of Twente, Enschede Prof. dr. J.G Grandjean, University of Twente, Enschede Prof. dr. C.J. Zeebregts, University Medical Center Groningen Prof. dr. R.H. Slart, University of Twente, Enschede Prof. dr. R.J. de Winter, University of Amsterdam

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Samenvatting
Interventie cardiologen worden regelmatig geconfronteerd met lastig te behandelen laesies door een complexe anatomie van kransslagaderen, dan wel door de aard van de laesies zelf. De huidige generatie medicijnafgevende stents is inmiddels erg verfijnd wat de behandeling van dergelijke patiëntenpopulaties kan verbeteren en wat mogelijk tot een verbetering van de klinische uitkomsten kan leiden. Studies naar de klinische uitkomsten van deze complexe patiënten na implantatie van nieuwere generaties medicijnafgevende stents zijn echter beperkt. Het doel van dit proefschrift is inzicht te geven in het functioneren van nieuwere generaties stents bij patiënten met een uitdagende anatomie van de kransslagaderen en de te behandelen laesie.

Hoofdstuk 1 dient als een algemene inleiding voor dit proefschrift en verstrekt achtergrondinformatie over de medicijnafgevende stents en diverse anatomisch uitdagende laesies, zoals aorto-ostiale laesies, coronaire dominantie en bifurcatie laesies.

Hoofdstuk 2 laat een nieuwe benadering zien om VEGF-receptoren (VEGFR) binnen plaques aan te tonen. VEGF is betrokken bij angiogenese, een proces dat ook bij plaquedestabilisatie plaatsvindt. Bij deze nieuwe methode werd gebruik gemaakt van near infrared fluorescentie in combinatie met Cy5.5 gelabeld single chain VEGF (scVEGF). Er werd vervolgens gekeken of de aanwezigheid van VEGFR geassocieerd is met plaque instabiliteit. Near infrared fluorescentie toonde een ongelijkmatige verdeling van VEGFR en accumulatie van scVEGF/Cy5,5 (zogenaamde hotspots) dat geassocieerd was met een hogere capillaire dichtheid en verminderde aantallen α-SMA-positieve cellen. Dit zijn kenmerken van plaque instabiliteit. De bevindingen ondersteunen dat scVEGF/Cy5.5 een geschikte indicator is voor plaque instabiliteit en een veelbelovend diagnostisch hulpmiddel voor risicoanalyse van hart- en vaatziekten.

Hoofdstuk 3 laat een casus zien met een unieke aspiratie van een intact coronair bifurcatie trombus. Dit illustreert mooi de pathofysiologische mechanisme van een trombus welk is ontstaan uit een geruptureerde plaque en die vervolgens heeft voorgezet in de aftakkingen van een bifurcatie.

Hoofdstuk 4 onderzocht de klinische impact van medicijnafgevende stents na implantatie in het rechter aorta-ostiale regio (het gebied tot 3 mm vanaf de aorta opening). Een totaal van 321 patiënten uit de TWENTE trial zijn uitsluitend alleen aan de rechter coronair arterie behandeld, waarvan 67 (20,9%) patiënten een implantatie van een stent in de aorto-ostiale regio hebben ondergaan. Een follow-up periode van 2 jaar laat zien dat patiënt bij wie een stent was geïmplanteerd in de rechter aorto-ostiale regio geassocieerd is met een hogere incidentie van target-lesion revascularisatie (TLR; 7,5% versus 1,6%; p=0,02). Na correctie van confounders, blijkt het implanteren van een stent in de aorto-ostiale regio een onafhankelijke voorspeller van TLR te zijn met een gecorrigeerde hazard ratio van 4,1 (95% CI: 1,17-14,39; p = 0,03). Dit hoofdstuk laat zien dat de behandeling van de rechter aorta-ostiale regio met tweede-generatie medicijnafgevende stents haalbaar is, echter blijft het een voorspeller van TLR.

Hoofdstuk 5 beschrijft de huidige status van de behandeling met de nieuwere generatie medicijnafgevende stents in coronair bifurcatielaesies. In dit hoofdstuk worden de behandelingen van deze specifieke laesies bediscussieerd en hieruit wordt geconcludeerd dat behandeling van bifurcatielaesies nog steeds een belangrijke toetssteen is voor nieuwere generaties medicijnafgevende stents en dat verder onderzoek nodig is om klinische uitkomsten hiervan inzichtelijk te maken.

Hoofdstuk 6 bestudeerde de lange termijn klinische uitkomsten na implantatie van twee veelgebruikte tweede generatie medicijnafgevende stents, de Resolute en Xience V. Onder de 1391 patiënten van de TWENTE trial, werden 362 (26%) patiënten behandeld voor bifurcatielaesies. Na 3-jaar follow-up was behoudens een hogere incidentie van peri-procedurele myocardinfarct bij patiënten die behandeld waren voor bifurcatielaesies (6.9% vs. 3.1%; p <0,01), geen verschillen gevonden in andere eindpunten. De incidentie van stent trombose was laag en vergelijkbaar voor beide groepen (0,8% vs. 1,8%; p = 0,22). Er was tevens geen verschil gevonden in het eindpunt target-vessel failure (een gecombineerd eindpunt bestaande uit cardiale dood, target-vessel gerelateerde myocardinfarct en klinisch geïndiceerde target-vessel revascularisatie) tussen de beide stents (13,6% vs. 12,6%; p = 0.78). Dit hoofdstuk laat zien dat ondanks een significant verschil tussen de groepen in peri-procedurele myocardinfarct, de 3-jarige klinische uitkomsten na de implantatie van de tweede generatie medicijnafgevende stents gunstig was en vergelijkbaar voor patiënten die wel of niet behandeld waren voor bifurcatielaesies. Daarnaast hebben we geen verschil gevonden in de lange termijn klinische uitkomsten tussen de Resolute en Xience V stent.

Hoofdstuk 7 bespreekt de relatie tussen een links coronair dominant systeem en het risico op het optreden van events na de implantatie van tweede generatie medicijnafgevende stents. Follow-up gegevens van 1387 patiënten uit de gerandomiseerde TWENTE trial werden geanalyseerd. Op basis van de oorsprong van de posterior aflopende kransslagader werd de coronaire circulatie onderverdeeld in het linker en niet-linker dominant systeem (of te wel rechts of gebalanceerd). Dit hoofdstuk laat zien dat na 2 jaar follow-up, patiënten met een links coronair dominant systeem geassocieerd worden met een verhoogde incidentie van peri-procedurele myocardinfarct (8,8% vs. 3,6%, p<0,01) en bleek ook een onafhankelijk voorspeller te zijn voor peri-procedurele myocardinfarct (adjusted HR 2,19; 95%CI:1,15-4,15, p<0.02), terwijl er geen verschillen werd gevonden in andere klinische eindpunten.

Hoofdstuk 8 onderzocht de klinische uitkomsten van patiënten die een tweede generatie medicijnafgevende stent hadden gekregen met een off-label indicatie (n = 1033) en vergeleek deze met de resultaten van patiënten die werden behandeld met een on-label indicatie (n = 358). Patiënten met ten minste één van de volgende criteria werden beschouwd als off-label patiënten: nierinsufficiëntie met serum kreatinine ≥140 µ mol/l; linkerventrikel ejectiefractie <30%; acuut myocardinfarct binnen 72 uur; >1 laesie/bloedvat behandeld; >2 bloedvaten behandeld; laesie lengte>27 mm; bifurcatie laesie; vene graft laesie; arteriële bypass graft laesie; in-stent restenose; unprotected hoofdstam laesie; laesie met trombus; laesie met een totale occlusie. Patiënten uit de off-label groep hadden een significant hogere incidentie op peri-procedurele myocardinfarct (5,0% vs.1.4%, p<0,01), vergeleken

met de patiënten uit de on-label groep. Dit hoofdstuk laat zien dat ondanks verschillen in de risico profielen van on- versus off-label patiënten, behoudens een toegenomen incidentie van peri-procedurele myocardinfarct, de andere klinische eindpunten vergelijkbaar zijn na implantatie van de tweede generatie medicatieafgevende stents. Deze bevinden benadrukken de gunstige veiligheidsprofiel van de tweede generatie medicijnafgevende stents.

Hoofdstuk 9 onderzocht de relatie tussen de Syntax score, een scoringssysteem dat de complexiteit van coronaire hartziekte weergeeft, en het optreden van een peri-procedurele myocardinfarct na implantatie van tweede generatie medicijnafgevende stents. Van de 1391 patiënten in de TWENTE trial, werd de Syntax score berekend bij 1243 patiënten (89,4%). De incidentie van peri-procedurele myocardinfarct was hoger bij patiënten in de hoogste tertiel groep van de Syntax score in vergelijking met de midden en laagste tertiel groepen (7,3% vs. 3,1% vs. 1,6%, p<0,01). Dit hoofdstuk toont de relatie tussen de mate van arteriosclerose, welk wordt weerspiegeld door een hogere Syntax score, en het risico van het optreden van een peri-procedurele myocardinfarct.

Hoofdstuk 10 onderzocht in 1709 patiënten van de TWENTE trial en de non-enrolled TWENTE registry, de impact van een eerdere coronaire bypassoperatie op de klinische uitkomst na implantatie met de tweede generatie medicijnafgevende stents. Van alle patiënten, hadden 202 (11,8%) een geschiedenis van eerdere coronaire bypassoperatie. Een follow-up van 1 jaar liet zien dat patiënten met een eerdere coronaire bypassoperatie geassocieerd waren met een hogere incidentie van target-vessel revascularisatie (9.4% vs. 2.3%, p<0,01), met name binnen de groep patiënten die behandeld waren voor veneuze graft laesies (p<0,01). Bij patiënten die behandeld werden voor natieve coronair laesies, werd niet een dergelijk verschil waargenomen.

Hoofdstuk 11 onderzocht de 1-jaar veiligheid en effectiviteit van twee ‘highly deliverable’ derde generatie medicijnafgevende Resolute Integrity vs. Promus Element in 1811 all-comers patiënten binnen de gerandomiseerde DUTCH PEERS trial. De ‘highly deliverability’ werd aangetoond doordat weinig patiënten werden behandeld met een niet-gerandomiseerde stent (6 patiënten (1%) in de Resolute Integrity groep en 5 (1%) in de Promus Element groep, p=0.22). In totaal kregen 55 (6%) patiënten van de Resolute Integrity groep en 47 (5%) van de Promus Element groep een target-vessel failure (primaire klinisch eindpunt) en was de non-inferioriteit van de Resolute Integrity vergeleken met de Promus Element aangetoond (pnon-inferioriteit p<0.01). Er was tevens ook geen verschil in individuele componenten van het primaire eindpunt. Het aantal patiënten met een definitieve stent trombose was laag en trad op in 3 (0.3%) patiënten binnen de Resolute Integrity groep en 6 (0,7%) binnen de Promus Element groep. Dit hoofdstuk demonstreert dat deze nieuwe generatie medicijnafgevende stents gelijkwaardig effectief en veilig zijn en toont een excellente klinische uitkomst na 1 jaar follow-up.

Hoofdstuk 12 onderzocht de 2-jaars klinische uitkomsten en de patiënt gerapporteerde pijn op de borst binnen de DUTCH PEERS trial, waarbij patiënten behandeld waren met Resolute Integrity of Promus Element. Twee jaar follow-up

data was beschikbaar in 99,9% van alle 1811 participanten. Het primaire klinische eindpunt, target-vessel failure, trad op in 8,6% binnen de Resolute Integrity groep en 7,8% in de Promus Element groep (p=0,55). Tijdens 1 en 2 jaar follow-up hadden meer dan 80% van de participanten geen klachten van pijn op de borst en waren daarin ook geen verschillen aangetoond tussen beide stents. Patiënten die na 12 maanden, tijdens matige dan wel milde lichamelijke inspanning of in rust pijn hadden op de borst, hadden een bijna twee keer zo hoge risico op een klinisch geïndiceerde target-vessel revascularisatie in het tweede jaar (HR: 1.89, 95% CI: 1.05-3.39, p = 0.03) vergeleken met patiënten die alleen bij maximale inspanning pijn op de borst hadden of helemaal pijnvrij waren. Dit hoofdstuk toont aan dat na twee jaar follow-up binnen de DUTCH PEERS trial, de klinische events laag en vergelijkbaar waren voor beide medicijnafgevende stents en dat de meerderheid van de patiënten na 1 en 2 jaar vrij waren van pijn op de borst.

Hoofdstuk 13 onderzocht de klinische uitkomsten van patiënten die werden behandeld met twee 'highly deliverable' medicijnafgevende stents (Resolute Integrity of Promus Element) in de setting van een acute myocardinfarct. Van alle participanten van de DUTCH PEERS trial, presenteerden bij inclusie 817 (45%) patiënten met een acute myocardinfarct. Tussen de stent groepen waren geen significante verschillen gevonden in met de klinische uitkomsten na tweejaar follow-up. De incidentie van target-vessel failure (7.4% vs. 6.1%; p=0.45), target-lesion revascularisatie (3.1% vs. 2.8%; p=0.79), en definite stent thrombose (1.0% vs. 0.5%; p=0.69) waren laag en vergelijkbaar tussen beide stent groepen. Dit hoofdstuk laat zien dat zowel de Resolute Integrity als de Promus Element veilig en effectief zijn bij de behandeling van patiënten met een acute myocardinfarct.

Hoofdstuk 14 introduceert de opzet en bediscussieerd de rationale van de reeds gestarte BIO-RESORT trial, een gerandomiseerde vergelijking van biodegradable en durable polymeer gecoate medicijnafgevende stents. In deze onderzoeker geïnitieerde, prospectieve, patiëntgeblindeerde, gerandomiseerde multicenter trial met 3540 all-comer patiënten, wordt de veiligheid en effectiviteit van twee nieuwe biodegradable polymeer gecoate medicijnafgevende stents, de Synergy en Orsiro, vergeleken met de durable polymeer gecoate Resolute Integrity stent, welk als referentie dient. De BIO-RESORT trial zal nieuwe inzichten geven voor wat betreft klinische uitkomsten van deze drie moderne medicijnafgevende stents. Tevens zal deze trial de impact onderzoeken tussen bekende en onbekende diabetes mellitus en de klinische uitkomsten daarvan.

Conclusie

Coronaire hartziekte is wereldwijd een groot gezondheidsprobleem. Het betreft een grote populatie, mede door vergrijzing, welk is geassocieerd met een verhoogde kans op arteriosclerose. Steeds meer onderzoeken laten zien dat arteriosclerose niet simpelweg een luminale vernauwing is van een bloedvat, maar dat complexe pathofysiologische mechanismen meespelen, zoals ontsteking, intraplaque hypoxie en angiogenese wat uiteindelijk kan leiden tot plaque destabilisatie, trombusvorming en het optreden van een myocardinfarct. Beeldvormende technieken zoals near infrared fluorescentie met scVEGF/Cy5.5 zijn veelbelovende diagnostische hulpmiddelen voor de risicoanalyse van hart- en vaatziekten.

Behandeling van obstructieve coronaire hartziekte met percutane coronaire interventie heeft veel belangrijke verbeteringen ondergaan, met name na de introductie van medicijnafgevende stents. Verschillende uitdagende anatomische kenmerken van de coronairen zijn in de loop van de tijd geïdentificeerd. Het gebruik van moderne (tweede generatie) medicijnafgevende stents heeft over het algemeen geleid tot een gunstige klinische uitkomst bij deze uitdagende groep patiënten. Binnen deze patiëntengroep vallen patiënten met een links dominant coronair systeem, bifurcatielaesies en laesies waarbij het rechter aorta-ostiale segment betrokken is. Ondanks dat bij patiënten met een links dominant coronair systeem en met bifurcatielaesies meer peri-procedurele myocardinfarcten voorkwamen, was dit niet geassocieerd met een slechtere prognose op langere termijn. De syntax score lijkt een veelbelovende instrument te zijn voor het identificeren van patiënten die een verhoogde kans hebben op het krijgen van een peri-procedurele myocardinfarct. Ondanks de technische verbeteringen van de nieuwere generaties medicijnafgevende stents, blijkt de uitgebreidheid van arteriosclerose een belangrijke voorspeller te zijn voor revascularisatie, bijvoorbeeld bij patiënten met een stent dat (deels) geïmplanteerd is in de rechter aorta-ostiale regio of bij patiënten die een eerdere coronaire bypassoperatie hebben ondergaan en nu opnieuw gedotterd werden in een veneuze graft laesie. Het gebruik van de tweede generatie medicijnafgevende stents in complexe patiënten (d.w.z. met een off-label indicatie) is uitvoerbaar en geeft gunstige klinisch uitkomsten behoudens een toegenomen risico op het krijgen van een peri-procedurele myocardinfarct.
De recentelijk ontwikkelde ‘highly deliverable’ medicijnafgevende stents, heeft de behandeling van coronaire hartziekte verder verbeterd. In de DUTCH PEERS trial, werden twee veel gebruikte ‘highly deliverable’ medicijnafgevende stents Resolute Integriteit vs. Promus Element onderzocht, en toonde een vergelijkbare veiligheid en effectiviteit met excellente klinische uitkomsten. Vergelijkbare resultaten werden tevens gezien in een hoog risico subpopulatie van patiënten die werden behandeld voor een acute myocardinfarct. Ook na een follow-up periode van 2 jaar, blijkt in de DUTCH PEERS trial, dat de klinische events laag en vergelijkbaar bleven en dat meerderdeel van de patiënten geen pijn klachten meer hadden op de borst.

Naast de ‘highly deliverable’ medicijnafgevende stents, zijn er ook ‘biodegradable’ polymeer gecoate medicijnafgevende stents ontwikkeld. Deze stents laten na het vrijgeven van de medicatie en resorptie van het polymeer een bare metal stent achter. Data over routinematig gebruik van dergelijke nieuwe stents zijn schaars. De reeds gestart BIO-RESORT trial vergelijkt twee nieuwe biodegradable polymeer gecoate stents, de Synergy en Orsiro, en vergelijkt deze met de Resolute Integrity dat een ‘durable’ polymeer coating heeft. De trial zal meer inzicht verschaffen over de klinische uitkomsten van deze moderne medicijnafgevende stents, welk zal bijdragen bij de ontwikkeling van nog betere coronair stents.

Intensive Care

The role of cell savers and filters in cardiac surgery

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
woensdag 25 november 2015 om 11:00 uur

door

Jan Wytze Vermeijden

geboren op 9 december 1972 te Haarlem

Promotores:	Prof. dr. T.W.L. Scheeren
	Prof. dr. M.A. Mariani
Beoordelingscommissie:	Prof. dr. C. Boer
	Prof. dr. J.G Grandjean
	Prof. dr. C.J. Kalkman

Samenvatting

Het doel van deze Nederlandse samenvatting is om diegenen die niet met dit onderwerp vertrouwd zijn, kennis te laten nemen van de inhoud van dit proefschrift getiteld: ”The role of cell savers and filters in cardiac surgery”, vrij vertaald als “De rol van cell savers en filters in de hartchirurgie”. Alvorens in te kunnen gaan op de inhoud van het proefschrift, zal ik eerst wat achtergrond informatie geven.

Voor een groot deel van de hartchirurgische operaties is het nodig om het hart van de patiënt (tijdelijk) stil te leggen. Dit geldt voor alle operaties aan de hartkleppen en voor een deel van de operaties waar omleidingen op de kransslagaderen (CABG= coronary artery bypass grafting) worden aangelegd. Tijdens zo’n operatie neemt een zogenaamde hart-longmachine de bloedsomloop van de patiënt over en voorziet de vitale organen (brein, nieren, lever) van voldoende bloed en zuurstof. Het hart en de longen van de patiënt worden dus omzeild (CPB= cardio-pulmonary bypass). Maar om het bloed door lichaamsvreemde materialen te kunnen laten stromen is het essentieel dat tijdens de hart-longmachine periode het bloed onstolbaar (anticoaguleren) wordt gemaakt met een bloedverdunner (heparine).

Maar als het bloed niet kan stollen, kan er ook veel bloedverlies tijdens de operatie optreden. Dit verloren bloed (shed blood) kan zich ophopen zowel in de holte waar het hart zich in bevindt (pericard en mediastinum), als ook in de ruimte waar de longen zich bevinden (pleuraholte). Weggooien van dit verloren bloed zou betekenen dat veel meer patiënten een bloedtransfusie zouden moeten krijgen. Bloedtransfusies worden in de hartchirurgie frequent gegeven. En hoewel deze levensreddend kunnen zijn, is ook bekend dat bloedtransfusies een negatief effect op de overleving van de patiënt kunnen hebben.

Een van de grote uitdagingen in de hartchirurgische praktijk is een manier te vinden om het verloren bloed zo veilig en eenvoudig mogelijk terug te geven aan de patiënt en tegelijk zo weinig mogelijk bloedtransfusies te geven.

Vanaf de jaren zeventig van de vorige eeuw werd het verloren bloed opgezogen en opgevangen in een reservoir (cardiotomie reservoir) en via de hart-longmachine weer teruggegeven aan de patiënt. Dit heet gebruik maken van cardiotomy suction. Nu blijkt het bloed dat op deze manier opgevangen en aan de patiënt terug gegeven wordt, vol te zitten met geactiveerde witte bloedcellen (leukocyten) en andere stoffen die de bloeddruk negatief kunnen beïnvloeden (vaso-active substancies) zoals vet en kleine micropropjes (micro-thrombi) die o.a. de bloedstolling, nieren en de hersenwerking negatief kunnen beïnvloeden. Om dit probleem van “niet-schoon bloed” te ondervangen, maar het bloed nog wel aan de patiënt terug te geven, is bedacht om een zogenaamde cell saver in te zetten. Er wordt dan geen of minder gebruik gemaakt van het cardiotomie reservoir.

Cell saving Cell saving is een techniek waarbij het bloed dat verloren gaat tijdens een operatie op te vangen (collect), het te verwerken (process) en daarna terug te geven aan de patiënt (retransfuse). Het opvangen en de verwerking van het bloed gebeurt door een daarvoor speciaal ontworpen apparaat, de cell saver. Dit apparaat is in eerste instantie bedacht om bloed, verloren tijdens niet-hartchirurgische operaties (zonder gebruik van de hart-long machine) terug te geven. Het bloed wordt onstolbaar gemaakt met heparine en opgevangen in een reservoir. Vervolgens wordt het bloed met hoge snelheid gecentrifugeerd en geconcentreerd. Dan wordt het gewassen met een fysiologische zoutoplossing. Door het centrifugeren blijven alleen de rode bloedcellen over die teruggegeven kunnen

worden aan de patiënt. Het plasma en de bloedplaatjes, dus de bloedstolling producten, gaan daarbij verloren. Door het wassen worden de laatste resten van leukocyten en plaatjes, de micro-thrombi vet, de heparine en vaso-active substancies verwijderd.
Filters Tijdens de hart-longmachine periode worden er normaliter al filters gebruikt zodat de micro-thrombi en vetdruppels niet in de bloedsomloop van de patiënt terecht komen. Er zijn de afgelopen jaren verschillende nieuwe filters ontwikkeld die specifiek leukocyten kunnen wegvangen (filtreren).
De duur van de hart-longmachineondersteuning aan een patiënt kan een activatie geven van leukocyten. Vooral het bloed dat zich een tijd in de holtes van hart en longen heeft bevonden kan hieraan bijdragen. Geactiveerde leukocyten scheiden stoffen af die een algemene ontstekingsreactie kunnen doen ontstaan (pro-inflammatoire reactie). Deze reactie is, hoewel bij ziekte gewenst, tijdens en na hartchirurgie juist ongewenst. Deze ontstekingsreactie kan er namelijk voor zorgen dat het bloed van een patiënt minder goed stolt na de operatie en dat de patiënt veel vocht of medicatie nodig heeft om de bloeddruk voldoende hoog te houden. Deze ongewenste ontstekingsreactie van de geactiveerde leukocyten kan (deels) voorkomen worden door het opgevangen bloed eerst door een leukocyten filter te laten lopen. De geactiveerde leukocyten worden dan in het filter gevangen en kunnen niet aan de patiënt teruggegeven worden. Het plasma en de bloedplaatjes, dus de bloedstolling producten, gaan hierbij niet verloren. Het is alleen niet bekend of deze techniek het aantal bloedtransfusies na hartchirurgie kan verminderen.
Onderzoeksvragen In dit proefschrift wordt daarom de rol van cell savers, filters en de combinatie daarvan op het verminderen van bloedtransfusies in de hartchirurgie onderzocht. Daarnaast wordt gekeken naar het effect van het gebruik van een cell saver of filter op de kwaliteit van het teruggegeven bloed.

Hoofdstuk 1
Dit hoofdstuk is een introductie van het proefschrift. Het beschrijft de verschillende mogelijkheden en problemen van de huidige bloedbesparende technieken in de hartchirurgie. Bloedbesparing is gewenst omdat, hoewel soms levensreddend, bloedtransfusies geassocieerd worden met een verhoogde morbiditeit en mortaliteit. Het gebruik van een cardiotomie reservoir wordt besproken. Het voordeel van een cardiotomie reservoir lijkt, hoewel niet bewezen, dat er minder bloedtransfusies gegeven worden. De nadelen van een cardiotomie reservoir zijn onder andere het teruggeven aan de patiënt van “niet-schoon bloed”.
De mogelijkheden van een filter als bloedtransfusie besparende strategie bij het gebruik van een cardiotomie reservoir worden besproken. Vervolgens wordt de rol van cell savers beschreven bij het verbeteren van de kwaliteit van het “cardiotomiebloed” en het verminderen van bloedtransfusies. Daarnaast wordt de bestaande literatuur over bloedbesparing door het gebruik van de cell saver in de hartchirurgie uitgebreid besproken. Hoewel de huidige consensus en aanbevelingen zijn dat een cell saver voordelig is om te gebruiken tijdens cardio-chirurgische operaties met een hart-long machine zijn er nog altijd aspecten die verduidelijking behoeven.

Hoofdstuk 2
Dit hoofdstuk beschrijft de multicenter (deelname van meerdere ziekenhuizen) en factoriaal (2 interventies worden zowel elk apart als in combinatie bestudeerd tegenover een groep waarbij geen interventie wordt toegepast) opgezette studie waarbij patiënten bij geplande cardio-chirurgische operaties met een hart-long machine gerandomiseerd verdeeld werden in vier groepen. Een groep waarbij een cell saver werd ingezet, een groep waarbij een cell saver met leukocytenfilter werd ingezet, een groep waarbij alleen het leukocyten-depletiefilter werd gebruikt om verloren bloed te bewerken en terug te geven. In de vierde groep werd de standaardbehandeling met cardiotomie-suction gebruikt. Wij tonen aan dat het gebruik van een cell saver tijdens de hartchirurgische operatie geen verlaging geeft van het totale aantal toegediende bloedproducten tijdens de ziekenhuis opname, maar dat het percentage patiënten die een bloedtransfusie kregen wel werd verlaagd. De bevindingen van dit onderzoek heeft klinische consequenties, want de transfusie van bloedproducten wordt geassocieerd met een vermindering van de lange termijn overleving en een verhoogde morbiditeit. De combinatie van een cell saver met het gebruik van een leukocyten-depletiefilter resulteerde niet in een klinisch relevant voordeel voor de patiënt evenmin als het filtreren van verloren bloed door een leukocyten-depletiefilter alleen. Onze bevindingen ondersteunen het gebruik van een cell saver tijdens hartchirurgische operaties met een hart-long machine. Tenslotte worden het effect van pre-operatieve bloedarmoede, hartchirurgische operaties en de bewaartijd van rode bloedcellen op intra-operatieve bloedtransfusies en post-operatieve mortaliteit besproken.

Hoofdstuk 3
Dit hoofdstuk beschrijft de klinische studie waarin wij onderzocht hebben of de kwaliteit van bloed verwerkt door een cell saver constant blijft. Afhankelijk van de hoeveelheid bloed die opgevangen wordt, kan een cell saver meerder malen tijdens dezelfde operatie ingezet worden (multiple runs). In deze studie hebben wij ook gekeken of opeenvolgende runs van een cell saver tijdens hart-chirurgische operaties met een hart-longmachine eenzelfde daling in de concentratie van het pro-inflammatoire cytokine IL-6 laat zien als een enkele processing run. Wat we vonden was dat met multiple runs de daling van de concentratie van IL-6 constant bleef. Hemoglobine, vrij hemoglobine, en hematrocriet bleken ook gelijk te blijven. Verder bleek dat met multiple runs er een concentratie effect van leukocyten optrad en de bloedplaatjes niet verschillend waren tussen de twee runs. Wij concluderen dan ook dat meerdere runs van een cell saver de kwaliteit van het bloed niet negatief beïnvloeden.

Hoofdstuk 4
Dit hoofdstuk beschrijft de studie waarin wij als onderzoeksgroep gekeken hebben naar het gebruik van een nieuw soort cell saver. Deze nieuwe cell saver kan behalve tijdens de hartchirurgische operatie, ook gebruikt worden om bloed verloren na de operatie op te vangen en na verwerking aan de patiënt terug te geven (post-operatieve autotransfusie). De verwachting was dat er een vermindering van het aantal bloedtransfusies zou kunnen worden bereikt als bloed verloren tijdens en ook na de hartchirurgische operatie met hart-longmachine aan de patiënt teruggegeven zou worden. Om te kijken of dit inderdaad bereikt is, vergeleken we twee groepen.

Een groep waarbij de cell saver alleen tijdens de operatie gebruikt werd en een groep waarbij het tijdens en na de operatie verloren bloed teruggegeven werd door de nieuwe cell saver. Wij lieten zien dat het gebruiken van de cell saver ook gedurende een specifieke tijd na de operatie op de intensive care geen verdere vermindering van bloedtransfusies geeft. Wat wij ook zagen is dat het post-operatief bloed opvangen en verwerken een toename geeft van een biologische marker die ook gebruikt wordt als indicator van hartspier schade, zonder dat er daadwerkelijke schade is opgetreden. Dit komt waarschijnlijk door hemolyse van het opgevangen bloed.

Hoofdstuk 5
Dit hoofdstuk beschrijft de prestaties van drie verschillende filters. Deze filters worden in de cardio-chirurgische praktijk gebruikt om geactiveerde leukocyten en vetdeeltjes uit bloed te halen/filteren dat teruggegeven wordt aan de patiënt tijdens een hartoperatie. De prestaties van twee specifieke voor leukocyten-depletie ontworpen filters en een vetfilter worden in een klinische situatie met elkaar vergeleken. Gekeken werd naar de doorlooptijd van het bloed, het aantal leukocyten en bloedplaatjes en de concentratie van totaal hemoglobine, triglyceride en vrije vetzuur in het bloed na het filtreren. Verder keken we naar vrij hemoglobine, plasma elastase (maat voor witte bloed cel activatie) en complement C5–9 (maat voor activatie stolling). Deze studie laat zien dat leukocyten-filters beter zijn in het filtreren van bloed ten aanzien van vet en witte bloedcellen in vergelijking met een vetfilter. Verder lieten wij zien dat het bloed sneller door een leukocyten-filter loopt, wat van klinisch belang kan zijn.

Hoofdstuk 6
Dit hoofdstuk gaat over het klinisch onderzoek dat we hebben uitgevoerd om te kijken of het gebruik van een cell saver tijdens hart-chirurgische operaties met een hart-long machine de rode bloedcel-functie negatief beïnvloedt. Patiënten die een hart-chirurgische operatie ondergingen, werden gerandomiseerd in een groep waarbij verloren bloed met een cell saver werd bewerkt en een groep waarbij het bloed zonder cell saver werd teruggegeven. In beide groepen werd er gekeken naar afgeleide parameters die informatie geven over de zuurstof-transportfunctie van de rode bloedcel. Dit zijn onder andere de vervormbaarheid en het 2,3-DPG gehalte. Wij concludeerden dat de vervormbaarheid en het 2,3-DPG gehalte van de rode bloedcellen verminderd wordt in vitro door het gebruik van een cell saver. Maar dat re-transfusie van dit bloed aan de patiënt in vivo de rode bloedcel-functie niet verder verslechterd. Verder lieten wij zien dat het gebruik van de hart-longmachine een negatief effect heeft op de klontering van de rode bloedcel, de vervormbaarheid en het 2,3-DPG gehalte.

Hoofdstuk 7
In dit hoofdstuk geven we een samenvatting van de beschreven studies en komen de conclusies uit het proefschrift naar voren. De eerste conclusie uit het proefschrift is dat het gebruik van een cell saver een nadelig effect kan hebben op de kwaliteit van de opgevangen rode bloedcellen, maar dat dit effect niet terug te vinden is in het bloed van de patiënt. Verder blijkt dat de kwaliteit van bloed, gemeten door afname van de pro-inflammatoire cytokine IL-6, door een cell saver niet afneemt als

er grotere hoeveelheden bloed opgevangen, gewassen en geconcentreerd wordt. De tweede conclusie uit het proefschrift is dat het gebruik van een filter als bloedbesparende techniek bij hartchirurgie met behulp van een hart-longmachine niet is aan te raden. De derde conclusie is dat het gebruik van een cell saver als bloedbesparende techniek tijdens hartchirurgie met een hart-longmachine wel kan worden aangeraden. Zelfs bij verwacht weinig bloedverlies omdat het gebruik van een cell saver de hoeveelheid patiënten die een bloedtransfusie krijgt, doet verminderen. Maar mogelijk draagt het gebruik van de cell saver eraan bij dat de totale hoeveelheid toegediende bloedproducten niet vermindert bij operaties met veel bloedverlies, door het verlies aan plasma en bloedplaatjes.
Aandachtspunten voor verder onderzoek zijn dat er nader gekeken moet worden naar het nut ten aanzien van het inzetten van een cell saver bij hartoperaties met een hartlongmachine met verwacht veel bloedverlies en naar de invloed van verschillende cell savers op het bloedbesparende effect. Verder is het van belang dat het cell saver-gebruik op een uniforme en complete wijze in komende studies beschreven wordt. Als laatste is het voor toekomstige studies van belang dat het gebruik van bloedproducten op een uniforme wijze wordt weergegeven.

Interne Geneeskunde

Female renal health:

translational studies on renal hemodynamics and the renin-angiotensin aldosterone system

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
maandag 9 februari 2015 om 14.30 uur

door

Tsjitske Jacoba Toering

geboren op 9 mei 1985

Promotor:	Prof. dr. G.J. Navis
Copromotores :	Dr. A.T. Lely
	Dr. M.M. Faas
Beoordelingscommissie:	Prof. dr. A.H.E.M. Maas
	Prof. dr. A. Franx
	Prof. dr. H. van Goor

Samenvatting
Men are from Mars, Women are from Venus. Het debat over psychosociale verschillen en overeenkomsten tussen mannen en vrouwen is van alle tijden. Tegenwoordig ontplooit deze discussie zich ook in de biomedische wereld. Waar stromingen in het feminisme het liefst de man en de vrouw als twee gelijken zien, begint de biomedische wetenschap steeds meer het belang te zien van de verschillen tussen de man en de vrouw. De huidige medische kennis is veelal gebaseerd op medisch onderzoek uit het verleden, dat voornamelijk en vaak exclusief bij mannen en mannelijke proefdieren werd uitgevoerd. Er komen echter steeds meer verschillen tussen mannen en vrouwen aan het licht in basale fysiologie, het voorkomen en progressie van ziekte en de respons op behandeling. Het ontrafelen van de (patho-)fysiologische mechanismen daarvan kan potentieel grote gevolgen hebben voor het dagelijks medisch handelen. Dit kan verhelderen waarom bepaalde ziekten vaker bij vrouwen dan bij mannen voorkomen (of andersom), en kan zich vertalen in geslachtsspecifieke behandelingen, waardoor een betere ziekte- en behandeluitkomst voor zowel mannen als vrouwen verwacht kan worden.

De verschillen tussen mannen en vrouwen zijn duidelijk aanwezig in het risico op hart-, vaat- en nierziekten. Vrouwen zijn voor de menopauze beschermd tegen het ontwikkelden van hart-, vaat- en nierziekten. Ook ligt de impact van bepaalde risicofactoren voor hart-, vaat- en nierziekten bij mannen anders dan voor vrouwen. Ten slotte bestaan er ook risicofactoren die alleen voor vrouwen gelden, namelijk degenen die gerelateerd zijn aan de zwangerschap en de complicaties daarbij, zoals pre-eclampsie (zwangerschapsvergiftiging). Pre-eclampsie is een zwangerschapsspecifieke ziekte die wordt gekenmerkt door hoge bloeddruk en proteïnurie in de tweede helft van de zwangerschap. Na een pre-eclampsie hebben vrouwen later in hun leven een verhoogd risico op hart-, vaat-, en nierziekten.

Waarom de risico's op hart-, vaat- en nierziekte verschillend zijn voor mannen en vrouwen, en waarom pre-eclampsie gepaard gaat met een verhoogd risico, is niet geheel duidelijk. Het renine-angiotensine-aldosteron systeem (RAAS), de renale hemodynamiek (lokale bloeddoorstomingsprofiel van de nier) en de volumeregulatie spelen een rol bij deze aandoeningen. De studies in dit proefschrift onderzoeken daarom de rol van het RAAS (**hoofdstuk 2-4**) en de verandering in renale hemodynamische functie en volume status (**hoofdstuk 5-7**) als mogelijk betrokken mechanismen.

DEEL I: DE ROL VAN HET RENINE-ANGIOTENSIN ALDOSTERON SYSTEEM

Verschillen tussen mannen en vrouwen in de respons op angiotensine II

Het RAAS is een hormoonsysteem dat een belangrijke rol speelt bij de regulatie van de bloeddruk, de renale hemodynamiek en de volume status. Er zijn geslachtsverschillen in de componenten en regulatie van het RAAS, die mogelijk van functioneel belang zijn. Er zijn aanwijzingen dat mannen en vrouwen verschillend reageren op therapie die gebaseerd is op het remmen van het RAAS. Bovendien zijn in dierstudies vrouwen minder gevoelig voor exogene stimulatie van het RAAS. Een belangrijk onderdeel van het RAAS is het hormoon angiotensine II (ang II). Ang II induceert vasoconstrictie in het centrale en perifere vaatbed en in de

nieren, en leidt tot een hogere bloeddruk. In **hoofdstuk 2** worden de geslachtsverschillen in de respons op ang II infusie in mensen en ratten bestudeerd. Bij de mens hadden mannen inderdaad een hogere bloeddruk respons op kortdurende infusie van ang II, met ook een sterkere vasoconstrictie in de nieren. Om na te gaan of sterkere ang II gevoeligheid op de langere termijn voor meer nierschade zorgt, onderzochten wij in ratten het effect van een 3 weken durende ang II infusie. Dit gaf bij mannetjes een snellere stijging in bloeddruk dan bij vrouwtjes, met bovendien meer proteïnurie en intrarenale inflammatie. Deze verschillen gingen echter niet gepaard met geslachtsverschillen in de mate van nierschade. Onze resultaten zijn consistent met de eerdere resultaten dat mannen een hogere ang II gevoeligheid hebben dan vrouwen. Dit zou een rol kunnen spelen bij het verhoogde risico op hart-, vaat- en nierziekten in mannen. Om aan te kunnen tonen dat de verschillen in ang II geïnduceerde proteïnurie en inflammatie ook daadwerkelijk resulteren in verschillen in nierschade op de langere termijn, lijkt het nodig om ang II infusie studies te verrichten over een langere periode of een hogere dosering ang II te geven.

Geslachtsverschillen in gevoeligheid voor ang II kunnen worden veroorzaakt door een verschil in expressie en functie van de ang II receptoren. Ang II oefent zijn effect voornamelijk uit door te binden aan de ang II type 1 (AT1) receptor, wat zorgt voor o.a. vasoconstrictie. In het RAAS is er echter ook een as, die remmend werkt op de AT1-as en o.a. voor vasorelaxatie zorgt. Hierbij is de AT2 receptor betrokken. Wij vonden bij vrouwtjes ratten een hogere expressie van AT2 receptoren in de nieren. Dit ondersteunt de aanname dat de AT2 receptor een rol speelt in de verminderde gevoeligheid voor ang II bij vrouwen. De resultaten van onze ex-vivo aorta experimenten bevestigen dit; we vonden een sterkere relaxatie na ang II stimulatie via de AT2 receptor in vrouwelijk ratten. Deze geslachtsverschillen in de regulatie van het RAAS, inclusief de aanwezigheid en functie van de AT2 receptor, zijn mogelijk betrokken in de geslachtsverschillen in het risico op nierziekten, en/of de respons op behandeling.

Van pre-eclampsie naar nierziekten: de rol van het renine-angiotensine aldosteron systeem en angiogenetische factoren

In **hoofdstuk 3** beschrijven we de rol het RAAS en angiogenetische factoren in de pathogenese van pre-eclampsie en hun mogelijke rol in de verhoogde gevoeligheid van vrouwen met pre-eclampsie voor nierziekten. Tijdens de normale zwangerschap is de gevoeligheid voor ang II sterk verminderd, wat o.a. zorgt voor een daling in bloeddruk, een toename van bloedvolume en een toename van bloedtoevoer naar de placenta. Tijdens pre-eclampsie is deze beschermende verminderde ang II gevoeligheid niet (geheel) aanwezig. De exacte verklaring voor dit fenomeen is niet duidelijk, gesuggereerd wordt dat een daling in ang 1-7 spiegels of een verhoogde expressie van AT1 receptor in de vaten en placenta een rol spelen.

Naast de verstoringen in het RAAS, wordt ook een disbalans tussen pro-angiogenetische en anti-angiogenetische factoren verondersteld in de pathogenese van pre-eclampsie. Angiogenese is een biologisch proces waarbij nieuwe bloedvaten gevormd worden. Het is aangetoond dat anti-angiogenetische factoren die bij pre-eclampsie betrokken zijn, zoals s-Flt1 en sEng, een aantal weken voor het begin van de klinische symptomen van pre-eclampsie verhoogd zijn in de

circulatie van de moeder. Verhoogde spiegels van sEng (een TGF-β co-receptor) en sFlt1 (een oplosbare vorm van vascular endothelial growth factor (VEGF) receptor 1) kunnen leiden tot endotheel dysfunctie bij de moeder met als gevolg hoge bloeddruk en proteïnurie. Ook het feit dat door het verhogen van de circulerende sFlt1 levels in zwangere muizen en ratten een syndroom ontstaat dat lijkt op pre-eclampsie, bevestigt dat sFlt1 een rol speelt in de pathogenese van pre-eclampsie. Het exacte mechanisme waardoor (anti)-angiogenetische factoren betrokken zijn bij de ontwikkeling van het typische renale fenotype tijdens pre-eclampsie is niet duidelijk.

Dierstudies suggereren dat de verstoringen in het RAAS-effect hebben op de sFlt1 productie, hetgeen suggereert dat er een interactie bestaat tussen dysregulatie van RAAS en van angiogene pathways bij de pathogenese van pre-eclampsie. Het is interessant te noemen dat patiënten met chronische nierziekten, zonder pre-eclampsie in het verleden te hebben doorgemaakt, ook verhoogde concentraties sFlt1 in het bloed hebben, wat positief correleert met proteïnurie. Blijkbaar komt de combinatie van verstoringen in het RAAS en de disbalans tussen pro- en anti-angiogenetische factoren ook bij chronische nierziekten voor; dit zou wellicht een rol kunnen spelen bij het verband tussen pre-eclampsie en het krijgen van chronische nierziekten. Om dit te onderbouwen, is het belangrijk om na te gaan of er na pre-eclampsie nog steeds een veranderde RAAS-activiteit of -gevoeligheid bestaat.

Het renine-angiotensine aldosteron systeem na pre-eclampsie
In **hoofdstuk 4** onderzochten we bij mensen en ratten of de verstoring in ang II gevoeligheid, die tijdens pre-eclampsie aanwezig is, ook na pre-eclampsie nog aanwezig is. Eerdere studies in vrouwen die hypertensie tijdens de zwangerschap of pre-eclampsie hebben gehad, vonden een verhoogde ang II gevoeligheid enkele jaren na de zwangerschap. Een kanttekening is dat de meeste vrouwen in deze studies comorbiditeit hadden (hypertensie, obesitas). De vraag rijst daarom of de associatie tussen de verhoogde ang II gevoeligheid na pre-eclampsie en een verhoogd renaal en cardiovasculair risico verklaard kan worden door pre-eclampsie zelf of door de onderliggende risicofactoren en comorbiditeit (zoals overgewicht, hypertensie, insuline resistentie en endotheel dysfunctie), mogelijk reeds aanwezig voor de zwangerschap. Tot nu toe wordt verondersteld dat pre-existente vasculaire/metabole risicofactoren zowel pre-eclampsie als hart-, vaat- en nierziekten veroorzaken. Daarom zou men kunnen stellen, zoals Sattar et al. hebben beschreven, dat zwangerschap een stresstest is waarbij subklinische hart-, vaat- en nierziekte aan het licht komen.

Om na te gaan of pre-eclampsie op zichzelf een causale factor is in de verhoogde ang II gevoeligheid in vrouwen die pre-eclampsie hebben gehad hebben wij in **hoofdstuk 4**, onder strikt gestandaardiseerde omstandigheden, ang II gevoeligheid onderzocht in gezonde vrouwen die pre-eclampsie hebben gehad en deze groep vergeleken met gezonde vrouwen die een normale zwangerschap hebben gehad. Bij een gelijke uitgangsbloeddruk, vonden we een trend naar een sterkere bloeddrukstijging tijdens ang II toediening in vrouwen die pre-eclampsie hebben gehad. Hoewel de verschillen subtiel zijn, suggereren onze bevindingen dat gezonde vrouwen, zonder comorbiditeit, die in het verleden pre-eclampsie hebben gehad nog steeds milde verstoringen in het RAAS hebben. Dit steunt de

veronderstelling dat pre-eclampsie zelf een blijvende verhoogde ang II gevoeligheid kan veroorzaken.

Vervolgens hebben we de oorzaak-gevolg relatie tussen pre-eclampsie en veranderde ang II gevoeligheid na de zwangerschap onderzocht in een zuiver model, namelijk in ratten na experimentele pre-eclampsie. In vergelijking met ratten na een gezonde zwangerschap of geen zwangerschap, was na experimentele pre-eclampsie de respons van bloeddruk en proteïnurie op ang II verhoogd. In de rat induceert experimentele pre-eclampsie zelf dus een verhoogde gevoeligheid voor ang II, die persisteert na de zwangerschap. In lijn met onze humane data suggereren deze resultaten dat, naast de risicofactoren die voor de zwangerschap aanwezig zijn, ook pre-eclampsie zelf een oorzakelijke rol speelt in het verhoogde risico op hart-, vaat- en nierziekten op de langere termijn.

Zoals al genoemd is het mechanisme achter de verhoogde ang II gevoeligheid tijdens en na pre-eclampsie niet geheel duidelijk. AT1-AA en sFlt-1 zijn mogelijk betrokken. Hladunewich et al. suggereren dat een veranderde balans tussen de AT1 receptor en AT2 receptor een rol speelt. Wij vinden eveneens een verandering in de regulatie van deze twee receptoren tijdens en na pre-eclampsie (**hoofdstuk 4**). In vaatcontractie experimenten in de thoracale aorta van ratten die pre-eclampsie hebben doorgemaakt, zien we een verminderde ex-vivo reactie van de AT2 receptor op ang II. Dit kan een verklaring zijn voor de verhoogde bloeddruk respons op ang II infusie die we zien bij deze ratten. We zagen geen verhoogde ex-vivo ang II respons via de AT1 receptor in de thoracale aorta, terwijl dit wel tijdens experimentele pre-eclampsie werd gezien. Het lijkt dus alsof de verhoogde ang II gevoeligheid tijdens pre-eclampsie door de AT1 receptor wordt geïnduceerd, terwijl na pre-eclampsie een verminderde werking van de AT2 receptor betrokken is. Zoals eerder beschreven, denkt men dat de AT2 receptor een rol speelt in de verminderde ang II gevoeligheid in vrouwen ten opzichte van mannen. Na pre-eclampsie lijkt het alsof de beschermende werking van deze depressor arm van het RAAS verminderd is. De consequenties van deze disbalans voor het krijgen van hart-, vaat- en nierziekten moet nog verder onderzocht worden.

DEEL II: DE ROL VAN RENALE HEMODYNAMIEK EN VOLUME STATUS

Renale hemodynamiek en de pathogenese van nierschade

Een van de hoofdfuncties van het RAAS is regulatie van doorbloeding van de nier, met name door het reguleren van de tonus in de efferente arteriole van de glomerulus. Glomeruli bestaan uit een kluwen capillairen (haarvaten), omgeven door een kapsel. In de glomeruli vindt de productie van voorurine plaats. De circulatie in de nier, en met name de glomerulus, kenmerkt zich door een unieke fysiologie. Zowel voor als na de glomerulaire capillairen bevindt zich een weerstandsvat, waardoor een zeer precieze regulatie van de druk in de glomerulus mogelijk is. Dit zorgt voor een constante filtratie van vocht in de glomerulus en tevens voor bescherming van het glomerulaire vaatbed tegen de schadelijke effecten van een verhoogde arteriële bloeddruk. Verstoring in de renale hemodynamiek kan dus op de korte termijn de perfusie in de nier en de glomerulaire filtratie beïnvloeden, maar kan tevens leiden tot structurele nierschade op de langere termijn door verlies van

bescherming van de glomerulaire capillairen, en daarnaast de volume status en daarmee bloeddruk en de belasting van het hart beïnvloeden. Omdat een verhoogde bloeddruk de hoofdoorzaak is van nierschade, maar nierschade zelf ook tot verhoogde bloeddruk leidt, kan een vicieuze cirkel ontstaan met uiteindelijk verdere achteruitgang van de nierfunctie. Deze inzichten zijn afkomstig van dierexperimenteel onderzoek uit de jaren 80, waarbij overtuigend bewijs werd gevonden over de pathogenetische rol van verhoogde glomerulaire druk in progressieve nierschade. In deze studies was ang II een belangrijke oorzaak van een te hoge efferente vaattonus en was RAAS-blokkade effectief om de vicieuze cirkel te doorbreken door een verlaging van de systemische en glomerulaire druk, waardoor de nier beschermd wordt tegen nierschade op de lange termijn.

In **hoofdstuk 5** geven we een overzicht van de huidige inzichten in de invloed van renale hemodynamische veranderingen op het lange termijn risico op nierziekte, en gaan we in op de veranderingen in renale hemodynamiek bij overgewicht. Overgewicht is een bekende risicofactor voor het krijgen van hart- en vaat- en nierziekten Overgewicht gaat vaak gepaard met hypertensie, en is vaak aanwezig bij vrouwen die pre-eclampsie doorgemaakt hebben. Gewichtstoename en een centrale verdeling van lichaamsvet (appelvorm) is geassocieerd met een verandering in renale hemodynamiek, namelijk een verhoogde glomerulaire filtratie (GFR) ten opzichte van de effectieve renale plasma flow (ERPF; nierdoorbloeding), wat resulteert in een verhoogde filtratie fractie (FF). Dit renale hemodynamische profiel vertoont kenmerken van glomerulaire hyperfiltratie en glomerulaire hypertensie, zoals in bovenstaande paragraaf beschreven. De veranderingen in renale hemodynamiek kunnen mee spelen in het verhoogde risico op nierschade bij overgewicht. Bij proefdieren is dit verband al lange tijd geleden aangetoond, maar bij de mens was een relatie tussen renale hemodynamiek en latere nierschade nog niet bewezen. Dat is overigens niet verwonderlijk: chronische nierschade ontwikkelt zich bij mensen over het algemeen in een proces van meerdere tientallen jaren, en tot zeer recent waren dergelijke langdurige follow-up gegevens voor mensen niet beschikbaar. Recent is echter ook bij de mens, in niertransplantatie patiënten, bewezen dat een hogere FF, als afspiegeling van hyperfiltratie, gepaard gaat met een hogere risico op nierschade op de lange termijn.

In mensen met overgewicht bestaat ook een verband tussen zouthuishouding en renale hemodynamiek. In jonge proefpersonen met een normale bloeddruk en overgewicht leidt een dieet met veel zout tot een stijging in FF, terwijl dit bij proefpersonen met een normaal gewicht niet het geval is. Dit gaat gepaard met een grotere toename van extracellulair lichaamsvocht (ECV) tijdens een hoog zout dieet in de proefpersonen met overgewicht. Bij overgewicht bestaat dus tijdens een ruime zoutinname zowel een lichte vorm van hyperfiltratie als een hoger ECV. De lange termijn consequenties van dit ongunstige hemodynamische profiel zijn niet bekend, maar theoretisch zou dit profiel bij kunnen dragen aan de ontwikkeling van zoutgevoelige hypertensie en hart- en nierschade op de langere termijn.

Geslachtsverschillen in renale hemodynamiek en volume status: de rol van het RAAS

Veel studies beschrijven verschillen in nierfunctie, bloeddruk en RAAS-activiteit tussen mannen en vrouwen. Echter, deze studies zijn moeilijk te interpreteren, omdat geen rekening gehouden wordt met het standaardiseren van zout intake of van fase van menstruele cyclus. Beiden zijn sterk van invloed op zowel nierfunctie, de bloeddruk als op het RAAS. Daarom hebben wij mannen en vrouwen vergeleken gedurende een gestandaardiseerde zout inname en met standaardisering van de fase van de menstruatiecyclus (**hoofdstuk 6**). Gedurende twee verschillende zoutinnames (hoog versus laag, beiden binnen de grenzen van wat in Nederland gebruikelijk is) werd de bloeddruk, nierfunctie en RAAS-activiteit in gezonde mannen en vrouwen onderzocht.

Wij vonden consistente verschillen tussen mannen en vrouwen in circulerende componenten van het RAAS. Voor een gegeven zout inname blijkt de plasma concentratie van het actieve renine (APRC) lager en de concentratie aldosteron hoger in mannen. De veranderingen die worden geïnduceerd door de verandering in zout intake (laag versus hoog) lopen parallel tussen mannen en vrouwen. De ratio tussen APRC en aldosteron is dus hoger in mannen dan in vrouwen, ongeacht de zoutinname. Deze verschillen kunnen veroorzaakt worden door verschillen in kalium intake, maar ook door het remmende effect van oestrogenen op de aldosteron productie in de bijnier bij vrouwen. Vergelijkbare data zijn verkregen in een populatie met hypertensie, en in een niet gestandaardiseerde/geselecteerde groep proefpersonen uit de algemene populatie, hetgeen onze bevindingen ondersteunt. Tot dusverre waren geen data bekend over de (patho-)fysiologische consequenties van de hogere aldosteronspiegel bij mannen. Wij vonden echter een hoger extracellulair volume (ECV) in mannen, gedurende beide zout condities, hetgeen suggereert dat de hogere aldosteron spiegel aanleiding geeft tot retentie van water en zout. Dit is bovendien geassocieerd met een hogere bloeddruk in mannen. Het hogere ECV kan ook het lage APRC in mannen verklaren, omdat volume expansie de renine afgifte onderdrukt. Bij mannen wordt de interactie tussen RAAS-activiteit en volume status dus gekenmerkt door een mild, subklinisch hyperaldosteronisme. Het is verleidelijk te speculeren dat dit verschil in RAAS-profiel betrokken is bij de geslachtsverschillen in het lange termijn risico op hart-, vaat-, en nierziekten. Een kanttekening is wel, dat de generaliseerbaarheid van onze data nog moet worden bewezen, en dat de vrouwen in onze studie maar in één fase van de menstruatiecyclus zijn bestudeerd.

Gedurende beide zoutinnames was de GFR na correctie voor lichaamsoppervlak niet verschillend tussen mannen en vrouwen. Echter, de ERPF was in vrouwen substantieel lager dan in mannen. Dit zou te maken kunnen hebben met het lagere ECV in vrouwen, omdat verschillen in volume status vaak leiden tot een parallelle verandering in de renale plasma flow, met daarbij een constante GFR. Daardoor wordt de FF hoger in vrouwen. Dit is lastig te rijmen met het risico op hart-, vaat- en nierziekten, dat juist bij mannen verhoogd is. Immers, een hogere filtratie fractie is geassocieerd met meer nierschade. Het is echter belangrijk op te merken dat het cardiorenale risico multifactorieel bepaald wordt en dat een enkele factor altijd geïnterpreteerd moeten worden in de context van de interactie met andere relevante

factoren. Het is voorstelbaar dat een stijging in FF door een lagere ERPF in de context van een lager ECV een aanpassingsmechanisme is zonder pathologische consequenties, terwijl een stijging in FF als gevolg van een hoog ang II gehalte of -gevoeligheid, of het verlies van structuur in het renale microvasculaire bed door een verlaging van de ERPF, wel schadelijk kan zijn op de langere termijn. Voor aldosteron geldt, bijvoorbeeld, dat hoge concentraties pas schadelijk zijn tijdens een grote overload aan zout, maar juist passend (en niet gerelateerd aan pathologie) tijdens een normale volumestatus en volume depletie. Over renale hemodynamiek zijn dergelijke data niet voor handen, maar onze bevindingen zouden daar wel een bijdrage aan kunnen leveren.

Renale hemodynamiek na pre-eclampsie
Er zijn enkele studies die laten zien dat bij vrouwen na pre-eclampsie zowel vroeg als laat na de zwangerschap de renale hemodynamiek afwijkend is, hetgeen bij zou kunnen dragen aan het risico op nierschade. In deze studies hadden de vrouwen echter naast pre-eclampsie ook hypertensie in de voorgeschiedenis. Hierdoor is de abnormale renale hemodynamiek niet met zekerheid aan de pre-eclampsie toe te schrijven, omdat ook hypertensie effect kan hebben op de renale hemodynamiek. Daarnaast is het ook hier weer belangrijk te noemen dat de renale hemodynamiek sterk wordt beïnvloed door de zouthuishouding en het RAAS. Daarom hebben wij in **hoofdstuk 7** het renale hemodynamische profiel in vrouwen, die tijdens de zwangerschap pre-eclampsie hebben doorgemaakt, onderzocht gedurende een laag en een hoog zout dieet. Alle deelnemers waren zorgvuldig geselecteerd op de afwezigheid van comorbiditeit. We vonden subtiele afwijkingen in de renale hemodynamiek bij vrouwen met pre-eclampsie in de voorgeschiedenis. De gevonden afwijking, een subtiel verhoogde FF, is consistent met een verhoogde glomerulaire druk. Onze resultaten ondersteunen een onafhankelijk effect van pre-eclampsie op de renale hemodynamiek na de zwangerschap.

Deze resultaten kunnen meer duidelijkheid geven over het onderliggende mechanisme dat ten grondslag ligt aan het verhoogde risico op nierschade op de langere termijn in deze groep vrouwen. Zoals beschreven in **hoofdstuk 5**, is een verhoogde FF een indirecte aanwijzing voor een verhoogde glomerulaire capillaire druk en daarbij gepaard gaat met een hogere risico op nierschade op de lange termijn. Het exacte mechanisme achter de verhoogde FF in vrouwen die pre-eclampsie hebben doorgemaakt kan bij de mens niet worden onderzocht, omdat daarvoor plaatselijke drukmetingen in de glomeruli nodig is. De verhoogde FF zou het gevolg kunnen zijn van hemodynamische of structurele veranderingen van de glomerulaire microvasculatuur, of een combinatie daarvan. Na pre-eclampsie vinden wij een iets verlaagde ERPF. Dit kan passen bij vasoconstrictie in de efferente arteriole van de glomerulus, of tenminste een verschil in efferent-afferente balans in vaattonus. Verschillende neurohumorale factoren kunnen zo'n patroon veroorzaken, zoals een verhoogde activiteit van het RAAS en het sympathische zenuwstelsel, vasopressine, natriuretische peptiden en/of andere factoren. Wij vonden echter geen verschillen in circulerende RAAS-parameters. Verschillen in intrarenale RAAS-activiteit zouden eveneens een rol kunnen spelen, maar de afwezigheid van verschil in renale respons op ang II maakt dit minder waarschijnlijk.

Conclusie

Onze resultaten bekrachtigen de noodzaak van nader onderzoek naar geslachtsverschillen in de regulatie van het RAAS, de regulatie van volumestatus en renale hemodynamiek. Hierdoor krijgen we beter inzicht in de geslachtsverschillen in het renaal risico profiel. Tevens kunnen vervolgens geslachtsspecifieke factoren meegewogen worden in de behandelrichtlijnen voor mannen en vrouwen, met als gevolg een betere gezondheidsuitkomst voor zowel mannen als vrouwen. Daarnaast kunnen we concluderen dat het belangrijk is vrouwen die pre-eclampsie in de voorgeschiedenis hebben, na de zwangerschap preventief te vervolgen om eventuele risicofactoren voor hart-, vaat-, en nierziekten op te sporen en behandeling toe te passen. Dit zouden bijvoorbeeld leefstijlrichtlijnen kunnen zijn of farmacologische interventies. Specifieke interventie studies bij vrouwen met pre-eclampsie in de voorgeschiedenis zijn noodzakelijk, zodat een betere lange termijn prognose ontstaat voor deze vrouwen.

Kindergeneeskunde

Exercise induced bronchoconstriction in childhood asthma

Development, diagnostics and clinical features

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
woensdag 18 februari 2015 om 14.30 uur

door

Janneke Carolien van Leeuwen

geboren op 9 februari 1984 te Oude Pekela

Promotor:	Prof. dr. E.J. Duiverman
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Samenvatting

Inspanningsastma, een tijdelijke luchtwegvernauwing na inspanning, is een veelvoorkomende manifestatie van astma bij kinderen. Inspanningsastma kan al op 3-jarige leeftijd voorkomen[1,2]. De kenmerken van inspanningsastma veranderen met de leeftijd[3,4] en worden vaak slecht herkend door kinderen, ouders en zelfs artsen[5,6]. Aan de andere kant kan inspanningsgebonden benauwdheid ten gevolge van bijvoorbeeld een slechte conditie ten onrechte worden geinterpreteerd als inspanningsastma, waardoor de diagnose astma onterecht wordt gesteld. Zodoende worden artsen geconfronteerd met vele uitdagingen in het herkennen, evalueren en behandelen van jonge kinderen met inspanningsastma. Dit proefschrift richt zich op onbeantwoorde vragen met betrekking tot de ontwikkeling, beoordeling en behandeling van inspanningsastma bij jonge kinderen.

Van bronchiolitis naar inspanningsastma

Hoofdstuk 1 is een algemene introductie waarin de huidige inzichten over de relatie tussen astma, inspanningsastma en virale luchtweginfecties worden besproken. In **hoofdstuk 2** worden de klinische kenmerken beschreven van kinderen jonger dan 2 jaar die met een virale luchtweginfectie (bronchiolitis) veroorzaakt door het respiratoir syncytieel virus (RSV) of rhinovirus (RV) in het ziekenhuis werden opgenomen. Bronchiolitis leidend tot ziekenhuisopname is een bekende risicofactor voor het ontwikkelen van astma[7-9]. RSV en RV zijn de meest voorkomende virussen die een bronchiolitis veroorzaken[10- 12]. Verschillende onderzoeken vergeleken al eerder de klinische kenmerken van RSV en RV bronchiolitis, maar de resultaten waren inconsistent[11,13,14]. Wij vergeleken symptomen in 120 opgenomen kinderen met een RSV of RV bronchiolitis en vonden geen significante verschillen in het klinisch patroon. Dus op klinische kenmerken zijn RSV en RV niet te onderscheiden en medische benadering zou daarom hetzelfde moeten zijn.

We onderzochten tevens de virale lading (CT-waarde) van RSV en RV en vonden een significante, maar zwakke, relatie tussen de virale lading en de opnameduur bij kinderen met een RSV bronchiolitis, terwijl de virale lading bij kinderen met een RV bronchiolitis niet was gerelateerd aan opnameduur.

De relatie tussen virale lading en klinisch patroon werd nader onderzocht in **hoofdstuk 3.** In dit hoofdstuk analyseerden we de dynamiek van de virale lading bij 103 kinderen opgenomen vanwege een RSV of RV bronchiolitis, door het bepalen van de CT-waarde tijdens ziekenhuisopname, ontslag en poliklinische controle. We bevestigden de in **hoofdstuk 2** beschreven relatie tussen virale lading bij ziekenhuisopname en totale opnameduur bij kinderen met een RSV bronchiolitis; hoe hoger de virale lading bij opname, des te langer de opnameduur. De virale lading van RSV daalde tijdens de ziekenhuisopname, wat ook in andere studies over virale lading van RSV bronchiolitis is beschreven[15-17]. Dus de virale lading van RSV bij ziekenhuisopname heeft potentieel waarde om het klinisch beloop van kinderen met een RSV bronchiolitis te voorspellen en vervolgen.

De virale lading van RV daarentegen liet geen relatie zien met opnameduur of ernst van de ziekte. Dit verschil in dynamiek van virale lading tussen RSV en RV infecties suggereert een verschillend pathofysiologisch mechanisme van beide virussen. De

gemiddelde virale lading bij ziekenhuisopname is significant lager bij RV bronchiolitis dan bij RSV bronchiolitis (**hoofdstuk 2 en 3**), wat deze hypothese ondersteunt. We speculeren dat bij RSV bronchiolitis de virale replicatie direct schade aan de luchtwegen teweegbrengt, wat de relatie van virale lading met opnameduur kan verklaren. Ziekteverschijnselen bij RV bronchiolitis zouden in meerdere mate gerelateerd kunnen zijn aan de ernst van de immunologische reactie van het lichaam op de infectie, waardoor er geen relatie tussen de RV virale lading en ziekteverschijnselen is. Genetische aanleg voor een immunopathologische reactie op RV infectie kan bijdragen aan de ontwikkeling van luchtwegproblemen op latere leeftijd. Dit kan de gesuggereerde sterke relatie tussen RV bronchiolitis en het ontwikkelen van astma verklaren[18,19].

Of er inderdaad een verschil is in het ontwikkelen van astma tussen kinderen met een verleden van RSV bronchiolitis en RV bronchiolitis werd onderzocht in **hoofdstuk 6.** In dit hoofdstuk beschreven we de prevalentie en ernst van inspanningsastma, een specifiek kenmerk van astma bij jonge kinderen. Zeventig 5-7-jarige kinderen met een voorgeschiedenis van ziekenhuisopname vanwege RSV of RV bronchiolitis op jonge leeftijd voerden een inspanningsprovocatietest uit. Deze test werd speciaal ontworpen om inspanningsastma bij jonge kinderen te onderzoeken (**hoofdstuk 5**). Bij 37% van de kinderen werd inspanningsastma vastgesteld. Dit is ongeveer 4 maal vaker dan de prevalentie van astma in een algemene groep Nederlandse kinderen jonger dan 12 jaar (maximaal 10%[20]). Het is belangrijk dat artsen zich bewust zijn van deze hoge prevalentie onder jonge kinderen met een voorgeschiedenis van bronchiolitis, mede gezien symptomen van inspanningsastma op deze leeftijd moeilijk te herkennen zijn[5,6]. Dit laatste werd bevestigd doordat ouders van de kinderen met een positieve inspanningsprovocatietest weinig inspanningsgebonden benauwdheidklachten rapporteerden. We vonden geen verschil in prevalentie of ernst van inspanningsastma tussen kinderen met een voorgeschiedenis van RSV bronchiolitis en RV bronchiolitis, hoewel in studies met oudere kinderen een gunstigere uitkomst na RSV bronchiolitis is beschreven[18,19,21,22]. De kinderen in ons onderzoek met een voorgeschiedenis van RSV bronchiolitis hadden juist een slechtere longfunctie dan de kinderen met een voorgeschiedenis van RV bronchiolitis. Een mogelijke verklaring voor de discrepantie tussen de uitkomsten na RSV en RV bronchiolitis kan liggen in het effect van leeftijd. De associatie tussen RSV bronchiolitis en het ontwikkelen van luchtwegproblemen neemt geleidelijk af met de leeftijd[23]; RSV bronchiolitis leidt tot een verhoogd risico op luchtwegklachten tot de leeftijd van 10, maar is niet meer significant op 13-jarige leeftijd[24]. De slechtere longfunctie gevonden bij de kinderen met een voorgeschiedenis van RSV bronchiolitis in ons onderzoek is compatibel met deze theorie. Het jonge kind met een matige longfunctie na RSV bronchiolitis heeft astmatische klachten, maar kan hier overheen groeien naarmate het ouder wordt; de luchtwegen zich ontwikkelen en luchtwegkaliber vergroot.

Het mechanisme dat de relatie tussen bronchiolitis en het ontwikkelen van astma op latere leeftijd verklaart is nog altijd een onderwerp van discussie. Sommigen speculeren dat bronchiolitis de luchtwegen beschadigt en/of de immunologische respons verandert, waardoor astma ontstaat. Anderen menen dat een bronchiolitis

simpelweg gepredisponeerde kinderen aan het licht brengt. Deze hypotheses sluiten elkaar echter niet uit en waarschijnlijk is het de combinatie van een ernstige luchtweginfectie in een pre-existent vatbaar kind wat leidt tot het ontwikkelen van astma op latere leeftijd[7].

Beoordeling van inspanningsastma bij jonge kinderen
Er bestaat een wijdverspreid geloof dat inspanningsastma ontstaat na het stoppen van inspanning. Artsen zijn daardoor geneigd astmatische symptomen tijdens inspanning als niet-astmatisch te beschouwen. Echter, bij kinderen met astma is de longfunctie 1 minuut na een reguliere inspanningsprovocatietest van 6 minuten vaak al substantieel gedaald, wat suggereert dat het begin van de luchtwegvernauwing al tijdens inspanning zou kunnen zijn. Bij volwassenen kan alleen langdurige inspanning (langer dan 15 minuten) luchtwegvernauwing tijdens inspanning uitlokken[25,26]. Longfunctie (FEV1) tijdens inspanning bij kinderen met astma is nog nooit onderzocht. In **hoofdstuk 4** maten we de longfunctie voor, *tijdens,* en na een verlengde inspanningsprovocatietest van 12 minuten bij 33 kinderen met astma in de leeftijd van 8-15 jaar. Terwijl de kinderen renden op een lopende band, maten we elke minuut tijdens inspanning de FEV1 tot een totale maximale testduur van 12 minuten of tot er een daling in FEV1>15% ten opzichte van de longfunctie voor inspanning optrad. Na inspanning werd longfunctieonderzoek herhaald. Van de 19 kinderen met inspanningsastma, gedefinieerd als een daling in FEV1>15% na inspanning, hadden 12 kinderen reeds luchtwegvernauwing *tijdens* inspanning. Dit zogenaamde ‘breakthrough inspanningsastma’ trad op tussen 6 en 10 minuten tijdens inspanning, met een verdere verslechtering van de FEV1 na stoppen van de inspanning.

Breakthrough inspanningsastma is waarschijnlijk het gevolg van een disbalans tussen luchtwegvernauwende en luchtwegverwijdende effecten tijdens inspanning. Naast luchtwegvernauwende effecten heeft inspanning luchtwegverwijdende effecten door afgifte van luchtwegverwijdende stoffen als stikstofoxide en prostaglandine en door oprekken van de gladde spiercellen ten gevolge van diepe ademteugen. Kennelijk is het luchtwegverwijdende effect van inspanning van korte duur bij kinderen met breakthrough inspanningsastma en wordt snel gevolgd door luchtwegvernauwing. Dit snelle optreden van breakthrough inspanningsastma bij kinderen is niet compatibel met de ‘thermale hypothese’, die stelt dat inspanningsastma wordt veroorzaakt door snelle opwarming van de luchtwegen na het stoppen van inspanning. Bij kinderen lijkt de osmotische hypothese, die inspanningsastma verklaart door uitdroging van de luchtwegen tijdens hyperventilatie, een belangrijkere rol te spelen. Het thermale fenomeen kan echter wel gedeeltelijk bijdragen aan inspanningsastma en zou het vertraagde herstel van luchtwegvernauwing bij oudere kinderen en volwassenen met astma kunnen verklaren.

De bevinding dat breakthrough inspanningsastma vaak voorkomt bij kinderen met astma is van klinisch belang. Breakthrough inspanningsastma kan resulteren in uitvallen tijdens sport, wat zelfvertrouwen verlaagt en leidt tot vermijden van inspanning met verslechtering van cardiovasculaire conditie tot gevolg. Artsen

moeten zich ervan bewust zijn dat kinderen met benauwdheidklachten *tijdens* inspanning zeer wel inspanningsastma kunnen hebben.

Breakthrough inspanningsastma is nader onderzocht in **hoofdstuk 5**. In dit hoofdstuk beschreven we een nieuwe inspanningsprovocatietest, ontwikkeld om inspanningsastma en breakthrough inspanningsastma bij 5-7-jarige kinderen te onderzoeken. Slechts weinig studies beschreven het bestaan van inspanningsastma bij kinderen jonger dan 8 jaar en deze studies vermeldden hoge mislukkingpercentages (~15%) van de inspanningsprovocatietests ten gevolge van moeilijkheden met longfunctiemeting en het volhouden van de inspanning[1]. Bij jonge kinderen wordt vaak gebruik gemaakt van vrij rennen om inspanningsastma te beoordelen, maar geforceerd rennen kan overweldigend zijn voor jonge kinderen en de inspanningsduur is gelimiteerd door de leeftijd[1]. Op zoek naar een geschikte vorm van inspanning die voor jonge kinderen te verduren, veilig en voldoende inspannend is om de hartslag boven 80% van de maximaal voorspelde waarde te houden (volgens internationale criteria), ontwikkelden we een inspanningsprovocatietest met behulp van een springkussen. De test bestond uit springen op een springkussen gedurende 6 minuten. Longfunctie werd gemeten voor, tijdens en na inspanning. Tweeentachtig kinderen voerden de inspanningsprovocatietest uit en alle kinderen waren enthousiast om te springen. Bij 7% van de kinderen kon de test niet betrouwbaar worden uitgevoerd, voornamelijk door moeilijkheden met het uitvoeren van de longfunctiemeting.

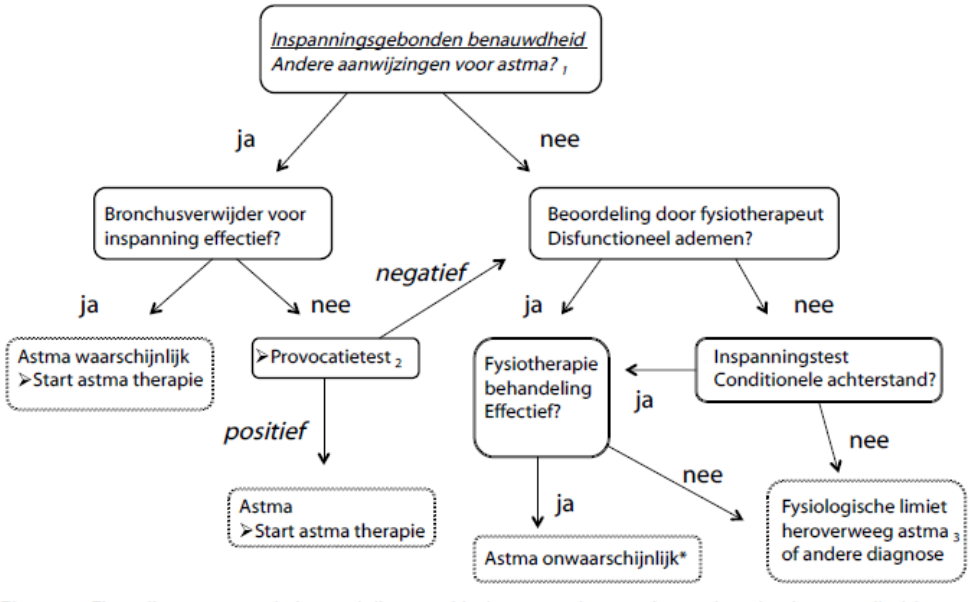
We concludeerden dat een inspanningsprovocatietest met een springkussen een geschikte, effectieve en veilige manier is om inspanningsastma bij jonge kinderen te diagnosticeren. Daarnaast toonde onze studie dat breakthrough inspanningsastma ook voorkomt bij jonge kinderen met astma. Bij jonge kinderen met breakthrough inspanningsastma daalde de gemiddelde longfunctie snel tijdens inspanning, soms al na 2 minuten. De kinderen met breakthrough inspanningsastma hadden een lagere longfunctie voor inspanning, een ernstigere daling in longfunctie na inspanning en een langzamer herstel van de luchtwegvernauwing vergeleken met de kinderen met niet-breakthrough inspanningsastma. Breakthrough inspanningsastma kan daarom beschouwd worden als een teken van slecht gecontroleerd astma, wat kinderen ernstig belemmert bij inspanning.

Het snelle optreden van breakthrough inspanningsastma bij jonge kinderen komt overeen met het leeftijdsgerelateerde beloop van inspanningsastma; hoe jonger het kind, des te korter de tijd tot maximale luchtwegvernauwing na inspanning en des te sneller het herstel van inspanningsastma[1,3,4,] wat onze studie bevestigde. Het verklarende mechanisme voor dit leeftijdsafhankelijke patroon is niet bekend. De luchtwegen van jonge kinderen drogen mogelijk sneller uit door hun relatief hoge ademminuutvolume en verminderde capaciteit om de inademingslucht te bevochtigen in vergelijking met volwassenen[27,28]. Snelle veranderingen in osmolariteit die hierdoor ontstaan resulteren waarschijnlijk in een snellere afgifte van ontstekingsmediatoren, die luchtwegvernauwing induceren. Daarnaast zouden de gladde spiercellen in de luchtwegen van jonge kinderen een verkorte reactie- en relaxatietijd kunnen hebben[3]. Deze ‘twitchiness’ van de luchtwegen neemt mogelijk

af naarmate het kind ouder wordt, de astmatische luchtwegen remodelleren en het gladde spiercel cytoskelet verstijft.

Hoofdstuk 8 is een review die uitdagingen behandelt die artsen kunnen tegenkomen in het herkennen en evalueren van inspanningsastma bij kinderen. In dit hoofdstuk worden aanbevelingen gedaan voor de beoordeling van inspanningsastma bij kinderen en adolescenten, gebaseerd op actuele literatuur.

Hoewel inspanning de klassieke astma symptomen kan uitlokken, kunnen symptomen in kinderen ook subtiel en niet-specifiek zijn. Ouder- en kind-gerapporteerde symptomen correleren zwak met de aanwezigheid en ernst van inspanningsastma[5,29], wat we ook in **hoofdstuk 5** beschreven. Daarom moeten vragenlijsten die astmacontrole bepalen aan de hand van gerapporteerde symptomen voorzichtig geinterpreteerd worden. Aan de andere kant worden inspanningsgebonden symptomen als gevolg van bijvoorbeeld disfunctioneel ademen, gebrek aan conditie, of andere cardiale of pulmonale ziekte, soms ten onrechte geïnterpreteerd als inspanningsastma. Zo hoesten bijvoorbeeld de meeste kinderen met inspanningsastma, maar dit symptoom is niet specifiek voor inspanningsastma[30]. De zwakke relatie tussen inspanningsgebonden symptomen en inspanningsastma benadrukt de noodzaak van het gebruik van provocatietests. Een suggestie voor de beoordeling van kinderen met inspanningsgebonden benauwdheid wordt gedaan in figuur 1.



Figuur 1. Flow diagram voor de beoordeling van kinderen met inspanningsgebonden benauwdheid. Uit *werkboek kinderlongziekten.* 1 Zoals allergische rhinitis, atopie, atopisch belaste familieanamnese, afwijkende longfunctie (afwijkende flow volume curve, reversibiliteit, FEV_1<70%). 2 Indirecte provocatietests zoals een inspanningsprovocatietest en mannitol test zijn specifiek voor astma. 3 Start flow diagram bovenaan en kies linker pad. *NB: astma en disfunctioneel ademen kunnen gelijktijdig voorkomen.

Een inspanningsprovocatietest is de eerste keus test om inspanningsastma bij kinderen vast te stellen, omdat het een “real-life” test is, die direct inzicht geeft in de ernst en het beloop van het inspanningsastma. De gebruikelijke protocollen voor inspanningsprovocatietests vereisen belangrijke aanpassingen voor het gebruik bij jonge kinderen, aangezien de tijd tot maximale luchtwegvernauwing en herstel van inspanningsastma bij kinderen leeftijdsafhankelijk is. Bovendien hebben jonge kinderen een korte aandachtsspanne en raken makkelijk vermoeid door herhaalde geforceerde longfunctiemetingen. We raden daarom aan om de longfunctiemetingen na inspanning nauwkeurig te timen, waarbij er in elk geval metingen in de eerste 5 minuten na inspanning verricht moeten worden om fout-negatieve uitslagen te voorkomen. Bij de meeste 3-7-jarige kinderen met inspanningsastma herstelt de longfunctie binnen 15-20 minuten, waardoor de longfunctiemetingen eerder gestopt kunnen worden dan in volwassen protocollen. Hoewel FEV1 de aanbevolen index is om inspanningsastma te diagnosticeren, lijkt de FEV0.5 bij kinderen jonger dan 7 jaar meer betrouwbaar, omdat de meeste jonge kinderen niet de vereiste geforceerde uitademing gedurende een hele seconde kunnen leveren[1,31,32]. Met een aangepast protocol kan een inspanningsprovocatietest reeds vanaf 3-jarige leeftijd worden uitgevoerd. Echter, soms zullen alternatieve provocatietests of longfunctiemetingen, zoals de geforceerde oscillatie techniek (FOT), nodig zijn om bronchiale hyperreactiviteit in kinderen te beoordelen.

Het beoordelen van de longfunctie tijdens inspanning om breakthrough inspanningsastma te diagnosticeren kan belangrijke informatie verschaffen over de ernst van het inspanningsastma. Bovendien kan het meten van breakthrough inspanningsastma ernstige en ongecontroleerde longfunctiedalingen, die soms optreden tijdens een reguliere inspanningstest, voorkomen. Een breakthrough inspanningstest zou mogelijk gebruikt kunnen worden als een dosis-respons provocatietest, waarbij de tijd tot het optreden van breakthrough inspanningsastma beschouwd kan worden als de mate van hyperreactiviteit.

Inspanningsastma en obesitas

Er zijn veel cross-sectionele onderzoeken die een associatie tussen overgewicht en inspanningsastma aantonen, echter er zijn geen prospectieve interventie studies verricht in kinderen. **Hoofdstuk 7** is een prospectief onderzoek naar het effect van gewichtsverlies door een dieet op inspanningsastma bij astmatische kinderen met overgewicht. Obesitas bij kinderen met astma is geassocieerd met ernstiger inspanningsastma vergeleken met niet-obese astmatische kinderen[33,34], maar het effect van gewichtsverlies was nog nooit in kinderen onderzocht. Twintig kinderen (8-18 jaar) met inspanningsastma en matig tot ernstig overgewicht volgden een dieet gebaseerd op een gezonde dagelijkse consumptie gedurende 6 weken. Voor en na de dieetperiode voerden ze een inspanningsprovocatietest uit. Naast een significante afname van gewicht en BMI, was het inspanningsastma significant verbeterd. De daling in BMI z-score was gerelateerd aan de verbetering van de longfunctiedaling in de kinderen die waren afgevallen.

Het gunstige effect van gewichtsverlies op inspanningsastma zou verklaard kunnen worden door een mechanische verbetering van adembewegingen en longvolumina, waardoor diepere ademteugen mogelijk zijn en dientengevolge gladde spiercellen in

de luchtwegen worden opgerekt. Gewichtsverlies kan ook leiden tot een afname van de systemische ontstekingsreactie, aangezien het lichaam van een patient met obesitas in een inflammatoire toestand verkeert met toegenomen concentraties van hormonen, chemokines en cytokines, die allemaal een rol spelen in luchtweginflammatie. De bevindingen dat zelfs een geringe afname van BMI inspanningsastma verbetert, impliceert het potentiele belang van gewichtsmanagement in de behandeling van het astmatische kind met overgewicht.

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Longgeneeskunde

Optimization of Nodule Management in Low-Dose CT Lung Cancer Screening

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
maandag 21 december 2015 om 14.30 uur

door

Marjolein Anne Heuvelmans

geboren op 26 december 1988 te Schijndel

Promotoren:	Prof. dr. M. Oudkerk
	Prof. dr. H.J.M. Groen
	Prof. dr. R. Vliegenthart
Beoordelingscommissie:	Prof. dr. H.J. de Koning
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Samenvatting
De interesse in het screenen van een hoog-risico populatie met lage-dosis CT (LDCT)-scans op longkanker neemt toe na publicatie van de positieve resultaten van de Amerikaanse National Lung Screening Trial (NLST) en de baseline resultaten van andere screening trials. In 2011 toonde de NLST aan dat jaarlijkse longkankerscreening met behulp van LDCT leidt tot een 20% afname in longkankerspecifieke mortaliteit, ten opzichte van de groep die jaarlijks gescreend werd met een thoraxfoto. Deze resultaten leidden tot een aanbeveling voor longkankerscreening van een hoog-risico populatie met periodieke CT-scans door verschillende Amerikaanse medische genootschappen, inclusief de Preventive Services Task Force.

Een nadeel van longkanker screening is het veelvuldig voorkomen van longnodules van kleine tot gemiddelde grootte (<500 mm^3). Tot 66% van de screeningpopulatie heeft tenminste een dergelijke nodule. Het overgrote deel van deze nodules is goedaardig. De meeste nodules die gevonden worden in longkanker screening zijn solide. Om goeden kwaadaardige nodules te kunnen onderscheiden is accuraat nodule management van groot belang. In de Nederlands-Belgische longkanker screeningstrial (NELSON studie, acronym voor Nederlands-Leuvens Longkanker Screening Onderzoek), is management van longnodules gebaseerd op volume van nodules gedetecteerd op baseline en nieuwe ontstane nodules in latere screeningsronden en op volume-verdubbelingstijd (VDT) van bestaande nodules op herhaalscans. De NELSON studie is de grootste gerandomiseerde studie waarin longkankerscreening door middel van LDCT wordt vergeleken met geen screening.

Longnodules met een groter volume of snelle groei hebben een grote kans om kwaadaardig te zijn. In de NELSON studie werden deelnemers met een nodule met volume <500 mm^3 of VDT <400 dagen doorverwezen naar een longarts voor nadere analyse. Deze unieke vorm van nodule management leidde tot een relatief laag percentage positieve screeningsuitslagen, terwijl het gemiste aantal kankers zeer klein was. Desalniettemin bleek het merendeel van de verdachte nodules die leidde tot verwijzing naar een longarts benigne nog steeds goedaardig te zijn.

Een nodule management protocol moet zorgen voor tijdige diagnose van longkanker, terwijl het aantal onnodige invasieve procedures voor goedaardige afwijkingen geminimaliseerd moet worden om angst, kosten en morbiditeit te voorkomen. Het hoofddoel van dit proefschrift was daarom om verschillende manieren te onderzoeken waarop het aantal fout-positieve screeningsuitslagen verder verkleind kan worden. De studies uitgevoerd in het kader van dit proefschrift dragen bij aan het optimaliseren van nodule management in LDCT longkankerscreening.

Dit proefschrift

Deel I: De huidige status van longkankerscreening in Europa
Ondanks dat longkankerscreening in de Verenigde Staten al aangeraden en uitgevoerd wordt in de algemene populatie, is het in Europa - tot nu toe - nog geen onderdeel van de dagelijkse praktijk. Er zijn verschillende longkankerscreeningstudies verricht in Europa, een deel daarvan is reeds afgesloten. De resultaten van deze studies en van de lopende Europese longkankerscreeningstudies worden besproken in **Hoofdstuk 2**. Momenteel heeft nog geen enkele reeds voltooide Europese longkankerscreeningsstudie een daling in longkankerspecifieke mortaliteit in de LDCT groep aangetoond. De resultaten van de grootste Europese longkankerscreeningtrial, de NELSON studie, worden naar verwachting echter pas in de loop van 2016/2017 bekend gemaakt. De tussentijdse resultaten van de NELSON studie werden in 2009 gepubliceerd. Het percentage positieve screeningsuitslagen binnen NELSON lag aanzienlijk lager dan die binnen de NLST (respectievelijk 2.6% op baseline en 1.8% in de tweede ronde versus 27.3% op baseline en 27.9% in de tweede ronde), met een vergelijkbaar hoge negatief voorspellende waarde (respectievelijk 99.7%-99.9% en 99.9%). Dit suggereert dat het relatief strenge op volume en VDT gebaseerde NELSON nodule management protocol, een protocol dat ook wordt gebruikt in de Duitse, Britse, en Deense longkankerscreeningstudies, efficiënter is en zou kunnen leiden tot minder screeningsgerelateerde comorbiditeiten en lagere kosten. Voordat er in Europa een positieve aanbeveling over longkankerscreening gedaan kan worden moeten er echter eerst een aantal vragen beantwoord worden over verschillen tussen een nodule protocol gebaseerd op diameter en op volume, namelijk over verschillen in vroege longkankerdetectie, morbiditeit, mortaliteit, expositie aan straling en kosten.

LDCT longkankerscreening omvat niet alleen de beoordeling van mogelijk kwaadaardige intrapulmonaal gelegen nodules; in 14% van de NELSON deelnemers werden extra-nodulaire aandoeningen zoals een aneurysma van de aorta of leverlesies gedetecteerd. Andere, veel voorkomende nevenbevindingen van longkankerscreening zijn calcificatie van de kransslagvaten en emfyseem. De twee grootste risicofactoren voor het ontwikkelen van longkanker, roken en leeftijd, hangen namelijk ook nauw samen met de ontwikkeling van deze ziektebeelden. In **Hoofdstuk 3** is een tienstappenplan voor de evaluatie van longkankerscreening CT's opgesteld dat niet alleen focust op het omgaan met gedetecteerde longnodules, maar ook op extra-nodulaire bevindingen.

Deel II: Kwantitatieve evaluatie van CT longkankerscreening
Zoals eerder beschreven moet een screeningsstrategie zeer sensitief zijn voor detectie van de ziekte, met een zo laag mogelijk aantal fout-positieven. Ondanks dat het aantal foutpositieve screeningsresultaten in de eerste twee screeningsronden van de NELSON studie al relatief laag was in vergelijking met andere, op diameter gebaseerde, screeningsstudies, was onze hypothese dat dit aantal nog verder gereduceerd zou kunnen worden na optimalisatie van afkapwaarden van de VDT van snelgroeiende longnodules. In **Hoofdstuk 4** werd aangetoond dat alle snelgroeiende longnodules in de NELSON studie die na de driemaandse herhalingsscan na baseline verwezen werden naar de longarts en kwaadaardig

bleken te zijn, een VDT hadden van ten hoogste 232 dagen. Dit suggereert dat verlaging van de VDT afkapwaarde voor snelgroeiende longnodules op korte termijn herhalingsscan na baseline het aantal fout-positieve testresultaten nog verder kan verlagen. Deze bevinding bleek niet toepasbaar op snelgroeiende nodules verwezen na de tweede ronde CT, een jaar na baseline, vanwege de grotere variatie van VDT's van maligne nodules gedetecteerd in deze incidentie screeningsronde.

In **Hoofdstuk 5** werd de optimalisatie van afkapwaarden van volume en VDT verder onderzocht, gebaseerd op de waarschijnlijkheid van kwaadaardigheid van een longnodule met bepaalde grootte of groeisnelheid. Het functioneren van dit vernieuwde protocol werd vergeleken met een diameterprotocol. Op baseline bleek de kans op kwaadaardigheid klein te zijn (0.6% [95% CI 0.4-0.8]) in longnodules met een volume van minder dan 100 mm^3 en deze kans bleek niet significant te verschillen van personen zonder longnodules (0.4% [0.3-0.6], *P*=0.17). De kans op longkanker was intermediair (2.4% [95% CI 1.7-3.5]; waardoor follow-up LDCT aanbevolen werd) wanneer nodules een volume tussen de 100 en 300 mm^3 hadden. Personen met een longnodule met een volume van minimaal 300 mm^3 hadden een significant grotere kans op longkanker vergeleken met personen zonder longnodules (16.9% [95% CI 14.1-20.0]; *P*<0.0001). Op basis van deze resultaten zijn nieuwe volume afkapwaarden voor screeningsgedetecteerde longnodules opgesteld.

In de huidige richtlijn voor het omgaan met door screening gedetecteerde longnodules van het American College of Chest Physicians (ACCP) worden nodules met een diameter <4 mm geclassificeerd als niet verdacht voor longkanker; nodules tussen de 4 en 8 mm worden geclassificeerd als intermediair (waarvoor beoordeling van groei (VDT < 400 dagen) geadviseerd wordt op een korte termijn LDCT); en nodules met diameter van minimaal 8 mm als verdacht voor longkanker. Alhoewel deze richtlijn goede resultaten liet zien op het gebied van sensitiviteit en specificiteit, hebben we aangetoond dat verbetering mogelijk is. Wanneer de diametergrens voor een negatieve screeningsuitslag verschoven werd van 4 naar 5 mm, voor een positieve screeningsuitslag van 8 naar 10 mm, en de VDT afkapwaarde voor nodulegroei van 400 naar 600 dagen, konden zowel een hogere sensitiviteit als specificiteit gemodelleerd worden. Voor het uitvoeren van deze analyses hebben we diameters gebaseerd op semiautomatische driedimensionale volumemetingen gebruikt, welke hoogstwaarschijnlijk meer accuraat zijn dan manuele diametermetingen, en daarom waarschijnlijk tot betere screeningskarakteristieken hebben geleid dan bereikt zou kunnen worden met manuele metingen. Indien er een volumeprotocol gebruikt werd (afkapwaarden 100 mm^3 en 300 mm^3, VDT grens van 600 dagen) werd een vergelijkbare sensitiviteit behaald als met het ACCP protocol, met een substantieel hogere specificiteit. De resultaten van deze studie impliceren dat het gebruik van een volumeprotocol in longkankerscreening vroege detectie van longkanker kan verbeteren en onnodige vervolgscans en invasieve diagnostische procedures kan verminderen.

Accurate schatting van nodulegrootte is van groot belang voor de optimalisatie van nodule management. In de meeste longkankerscreening richtlijnen wordt nodulegrootte gedefinieerd als gemiddelde nodule diameter (gemiddelde van lengte en breedte) op axiale CT-beelden. Hierbij wordt er vanuit gegaan dat een

longnodule redelijkerwijs gerepresenteerd wordt door een bolvorm, danwel ellipsoïde. Aangezien de natuur meestal geen perfecte, bolvormige, longnodules creëert, zullen fouten in de schatting van nodulegrootte optreden. Enkele studies gebruikten software om semiautomatisch driedimensionaal het nodulevolume te schatten. Het is aangetoond dat metingen met deze software leidden tot een grotere precisie en een kleinere meetfout, en een hogere betrouwbaarheid (betere overeenstemming tussen herhaalde metingen) dan manuele diameter metingen. De overeenstemming tussen diameter en volumemetingen voor de schatting van nodulegrootte werd geëvalueerd in **Hoofdstuk 6**. Hiervoor gebruikte we meetgegevens van 2240 solide nodules van intermediaire grootte, gedetecteerd op de baseline scan. In dit hoofdstuk wordt aangetoond dat de range in nodulediameter binnen verschillende volumecategorieën (50-100 mm^3, 100-200 mm^3, 200-300 mm^3, 300-400 mm^3, and 400-500 mm^3) enorm is: tot 11.0 mm voor maximale axiale diameter binnen nodules met een volume tussen de 50 en 100 mm^3. Het verschil tussen minimale en maximale diameters binnen een enkele nodule werd gedefinieerd als intra-nodulaire diametervariatie. Overall werd een mediane intranodulaire diametervariatie van 2.8 mm gevonden. Daarnaast hebben we aangetoond dat nodule volume berekend op basis van semiautomatisch verkregen gemiddelde of maximale diameter, uitgaande van een perfecte bolvorm van de nodule, leidt tot een substantiële overschatting van nodule grootte van respectievelijk 47.2% en 85.1%, vergeleken met semiautomatisch verkregen volume. Nodulediameter representeert nodulegrootte slecht; een nodule heeft een oneindig aantal ‘diameters’, maar slechts een volume. Daarom raden we aan om semiautomatisch verkregen volume en VDT te gebruiken in protocollen voor solide longnodules.

Nieuwe solide nodules zijn een veelvoorkomende bevinding in LDCT longkankerscreening en dragen een substantieel hoger risico kwaadaardig te zijn. Een gedetailleerde evaluatie van nodules voor het eerst gedetecteerd in de tweede of derde screeningsronde (gedefinieerd als incidente nodules) werd beschreven in **Hoofdstuk 7**. In de tweede en derde NELSON ronde werden 1222 nieuwe nodules in 787 personen geregistreerd. Uiteindelijk bleek 6.2% van deze nodules kwaadaardig te zijn. Het merendeel omvatte adenocarcinomen (38.0%), plaveiselcelcarcinomen (22.0%) en kleincellige longkankers (10.0%) en de meeste kankers werden gediagnosiceerd in stadium I (68.0%). Op moment van eerste detectie verschilde het mediane volume van kwaadaardige (296 mm^3, IQR: 73 - 721 mm^3) en goedaardige (39 mm^3, IQR: 21 - 103 mm^3) nieuwe solide longnodules significant (P<0.001).

Over de eerste drie screeningsronden van de NELSON studie werd in totaal een kankerpercentage van 2.6% gevonden (200/7582, inclusief de 50 kankers in nieuwe solide nodules). Nieuwe solide nodule dragen dus een aanmerkelijk hoger kankerrisico vergeleken met nodules die reeds aanwezig waren op de baseline scan. Daarom zullen in de toekomst strengere richtlijnen overwogen moeten worden voor nodules die pas na baseline gedetecteerd worden. Nieuwe nodules moeten agressiever vervolgd worden, waarbij een lagere afkapwaarde gebruikt moet worden voor een negatieve nodule (30 mm^3) en een korter screeningsinterval tussen twee

screeningsscans verkozen moet worden voor personen met een kleinere nieuwe nodule.

Er is weinig informatie beschikbaar over groeipatronen van longkankers, aangezien longkanker meestal pas in een laat stadium gediagnosticeerd wordt wanneer directe behandeling reeds noodzakelijk is. Longkankerscreeningsstudies waarbij longnodules in een deel van de gevallen met meerdere CT-scans vervolgd worden voordat de diagnose longkanker gesteld wordt bieden daarom een unieke kans om longkankergroei te bestuderen. In **Hoofdstuk 8** hebben we groeipatronen van 47 solide longkankers die gedetecteerd zijn in NELSON deelnemers en die vervolgd zijn met minstens drie LDCT-scans voordat de diagnose longkanker gesteld werd geëvalueerd en gekwantificeerd. De groeicurves volgden de exponentiele functie excellent, met een mediane R2 van 0.98 (IQR: 0.94-0.99). Daaruit konden we concluderen dat longkanker volume meestal toeneemt volgens een exponentiele functie. Deze studie is de eerste studie die het exponentiele groeipatroon van longkankers heeft kunnen kwantificeren en heeft kunnen aantonen dat longkankergroei beschreven kan worden middels de VDT.

Deel III: Kwalitatieve analyse van CT scans in longkankerscreening
Het NELSON protocol stond radiologen toe om in de praktijk naar eigen inzicht het screenresultaat dat gegeven zou moeten worden op basis van het NELSON protocol aan te passen, bijvoorbeeld in het geval van falende segmentatie door de software of hoge verdenking op kanker of juist een goedaardige afwijking. In de optimalisatie van de efficiëntie van screening is niet alleen sensitieve noduledetectie, maar ook accurate noduleclassificatie van groot belang. De invloed van de radioloog op de screeningsresultaten, door de beslissing af te wijken van het NELSON protocol, werd beschreven in **Hoofdstuk 9**. Radiologen besloten het screeningsresultaat te overrulen in 195 van de 3318 deelnemers (5.9%) waarin het screeningsresultaat gebaseerd werd op een solide of partieel solide longnodule. Van deze aanpassingen omvatte 95.4% een down-classificatie van positief naar intermediair of negatief, of van intermediair naar negatief. In geen van deze gevallen werd later toch longkanker gediagnosticeerd. Deze aanpassingen zorgden voor een verlaging van vervolgscans (n = 119) en directe verwijzingen naar de longarts (n = 67) en een verlaging van fout-positieve baseline screenresultaten van 22%. In twee van de negen gevallen met een upward-classificatie werd longkanker gediagnosticeerd. Daarom werd geconcludeerd dat de radioloog noduleclassificatie kan verbeteren, in toevoeging op een screeningsprotocol.

Het merendeel van de nodules van intermediaire grootte is goedaardig en zijn bijvoorbeeld granulomateuze of infectieuze laesies of vergrote lymfeklieren die naar verloop van tijd vanzelf weer verdwijnen. Onnodige vervolgscans en invasief onderzoek, kosten en angst bij de patiënt kunnen vermeden worden wanneer specifieke eigenschappen gevonden worden die nodules die vanzelf weer zullen gaan verdwijnen nauwkeurig kunnen identificeren. Het spontaan verdwijnen van longnodules in de NELSON studie is onderzocht in **Hoofdstuk 10 en 11**. Op baseline hadden 805 van de 7557 NELSON deelnemers (10.7%) tenminste een solide nodule van intermediaire grootte (totaal 964 nodules); in totaal verdwenen 97 nodules spontaan (10.1%). Alhoewel het overgrote merendeel van de longnodules

van intermediaire grootte gedetecteerd op baseline niet verdwijnt, vonden we dat driekwart van de nodules die wél verdwijnen reeds verdwenen zijn op het moment van de driemaandse herhaalscan na baseline. Helaas bleek dat verdwijnende longnodules CT eigenschappen deelden met kwaadaardige nodules (vaker een niet-gladde begrenzing). Daarom zijn nodule-eigenschappen niet geschikt om te voorspellen welke longnodules in de toekomst zullen verdwijnen.

In **Hoofdstuk 12** worden de hoofdresultaten van dit proefschrift op een rij gezet en bediscussieerd, worden de implicatie van de bevindingen, zowel voor nodules gevonden binnen longkankerscreeningsprogramma's als voor nodules gedetecteerd in de dagelijkse praktijk besproken en worden suggesties gegeven voor toekomstig onderzoek. Op basis van de onderzoeken in dit proefschrift kan worden geconcludeerd dat management van longnodules gedetecteerd in het kader van longkankerscreening op verschillende manieren kan worden verbeterd. Ten eerste door het gebruik van semiautomatische volumemetingen in plaats van manuele diametermetingen; ten tweede door gebruikt te maken van de VDT om nodulegroei te kwantificeren; ten derde door het optimaliseren van afkapwaarden voor volume en VDT om onderscheid te maken tussen negatieve, intermediaire en positieve screeningsuitslagen; ten vierde door aparte, strengere, richtlijnen op te stellen voor nieuwe nodules; en ten vijfde door ervaren thoraxradiologen in te zetten voor de beoordeling van screeningsscans en hun toe te staan in bepaalde gevallen van het screeningsprotocol af te wijken.

Of longkankerscreening al dan niet ingevoerd zou moeten worden in de dagelijkse praktijk in Europa zijn onder andere de uitkomsten van de mortaliteitsanalyses van met name de NELSON studie en tevens de overige lopende Europese longkankerscreeningsstudies van immens belang.

Revalidatiegeneeskunde

Design of a Robot-Assisted Gait Trainer:

LOPES II

Academisch Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Twente
op gezag van de Rector Magnificus
prof. dr. E. Brinksma
ten overstaan van een door het college voor promoties ingestelde
commissie, in het openbaar te verdedigen in de Agnietenkapel
op vrijdag 13 november 2015 om 16.45 uur

door

Johannes Hendricus Meuleman

geboren op 9 april 1976 te Amsterdam

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Samenvatting
In de laatste twee decennia heeft robotisch ondersteunde looptraining een sterke ontwikkeling doorgemaakt. Het gebruik van revalidatierobots in de klinische praktijk is echter beperkt. Belangrijkste oorzaken hiervan zijn de beperkte effectiviteit en de beperkte efficiëncy. De voornaamste twee uitdagingen in de ontwikkeling van robotisch ondersteunde looptraining zijn om tijdens training alleen te ondersteunen daar waar nodig, *Assist As Needed (AAN)* en het verlengen van de effectieve trainingstijd, voornamelijk door het verkorten van de tijd die nodig is om de patiënt te (de-)installeren in de robot (*donning doffng time*). AAN training houdt in dat de patiënt voldoende vrijheid moeten hebben tijdens het lopen en daarbij alleen ondersteuning krijgt bij specifieke (aangedane) aspecten van het lopen. Dit houdt vervolgens in dat de robot vrij moet kunnen bewegen in meerdere graden van vrijheid, Degrees of Freedom, (DoFs), en dat de aangedreven DoFs in staat zijn om de beweging van de patiënt te volgen, en een minimale weerstand, minimal impedance geven, m.a.w. ze moeten transparant zijn.

Na uitgebreid onderzoek naar de eisen gesteld door de eindgebruikers (fysiotherapeuten, revalidatieartsen, patiënten en onderzoekers) zijn de systeemvereisten voor de nieuwe robotische looptrainer, LOPES II, vastgesteld: een robot met een loopband, met het mechanisme achter de patiënt, met een minimum aantal bevestigingen aan het lichaam. Verder moet de patiënt vrij kunnen bewegen in rotaties en translaties van alle segmenten en gewrichten en de armzwaai moet ongehinderd zijn. In een onderzoek hebben we aangetoond dat men ongehinderd kan lopen als er tot 6 kg massatraagheid wordt toegevoegd aan het bekken of 2 kg massatraagheid aan de voet. Ondersteuning moet worden geleverd op het bekken in horizontale translaties, heup abductie/adductie (been zijwaarts) en flexie/extensie (bovenbeen voorwaarts/achterwaarts zwaaien), knie flexie/extensie en voet plantairflexie/dorsaalflexie (voetafzet/tenen optillen).

Tijdens de conceptfase hebben de eindgebruikers regelmatig de concepten geëvalueerd. Dit proces leidde niet alleen tot verbetering van de kwaliteit van de concepten, maar vergrootte ook de betrokkenheid van de eindgebruikers in het ontwikkelingsproces. De beste concepten werden geïntegreerd in een eenbenige mechanische proefopstelling. Deze opstelling heeft een gepatenteerde schaduwbeenbenadering, d.w.z. een mechanisch been achter de patiënt. Het schaduwbeen en het been van de patiënt zijn met elkaar verbonden met trekduwstangen. In tegenstelling tot conventionele robotische looptrainers met een mechanisch been aan de zijkant van het been van de patiënt, vergt het schaduw been mechanisme weinig afstelling. Het aantal bevestigingen is minimaal: een klem in het bekken (gecombineerd met een harnas voor de veiligheid en het leveren van gewichtsondersteuning), klemmen op de onderbenen (vlak onder de knieën), en klemmen bij de voeten (voetbakjes). Voor de bevestigingen bij de voeten en het bekken gebruiken we gepatenteerde gimbals welke rotaties van voeten en bekken toelaten en zorgen dat ondersteunende krachten aangrijpen in het midden van het enkelgewrichten en heupgewrichten. Verder bevat de proefopstelling een stoel waarop de patiënt kan zitten tijdens de (de-)installatie van de robot en om te rusten tussen de trainingen.

De geïntegreerde proefopstelling vormde, samen met een lijst van systeemvereisten, de input voor het ontwerp van de mechatronische prototypes. De mechanische structuur is zodanig ontworpen dat aangedreven graden van vrijheid grotendeels ontkoppeld zijn om complexiteit in berekeningen van de transformaties te voorkomen en om een optimale bewegingsvrijheid per graad van vrijheid te realiseren. De geselecteerde actuatoren zijn in staat om voldoende steun te leveren aan ernstig aangedane patiënten en ze zijn snel genoeg om bewegingen van snel lopen te kunnen volgen. Voor de aansturing van LOPES II hebben we voor *admittance control* gekozen. Hiermee kan zowel een hoge impedantie (veel ondersteuning) als lage impedantie (minimale ondersteuning) kan worden gegeven, doordat deze controller een (lage) virtuele massa weergeeft zonder wrijving. Speciaal ontworpen kracht sensoren vlakbij de bevestigingen geven input voor de admittance controller. Voor de veiligheid zijn er redundante kracht en positie sensoren aangebracht, om defecten van sensoren op te detecteren. De ontwikkeling van de stoel is niet meegenomen in dit ontwerp, om de primaire functie van LOPES II, d.w.z. ondersteuning bij het lopen, eerst goed te ontwikkelen.

Twee mechatronische prototypes zijn gebouwd en geïnstalleerd in het Roessingh Centrum voor Revalidatie in Enschede en de Sint Maartenskliniek in Nijmegen. Het mechanisme van de voet plantairflexie/dorsiflexie bleek, vanwege het gewicht, een nadelige invloed te hebben op de aansturing van de overige graden van vrijheid. Daarom is het mechanisme voor de voetafzet verwijderd. In plaats daarvan hebben we een passieve teen lifter toegevoegd die kan worden gebruik door patiënten met problemen met het optillen van de voet (bijvoorbeeld ten gevolge van zwakte in de dorsiflexor spieren of spasmen).

Vervolgens zijn we begonnen met de evaluatie van LOPES II, te beginnen met de verificatie van de systeemeisen. Na metingen van de mechanische stijfheid tussen de actuatoren en de krachtsensoren is gebleken dat LOPES II niet zo stijf is als vereist. Verder hebben we de positie nauwkeurigheid van LOPES II gemeten, d.w.z. hoe nauwkeurig kan LOPES II de gewrichtshoeken meten op basis van de gemeten motor hoeken. De gemeten fouten zijn kleiner dan de standaard deviatie van normaal lopen.

Voor de meeste graden van vrijheid is de impedantie van LOPES II voldoende laag. In de minimale impedantie modus, geeft de admittance controller een virtuele massatraagheid met een beetje demping. Voor de enkel translaties (anterior/posterior en mediolateraal) voegt LOPES II iets meer dan de toelaatbare 2 kg toe. Voor de knie anterior/posterior translatie voegt LOPES II 4:7 kg toe; iets meer dan de toelaatbare 4 kg. Echter, voor de bekken translaties voegt LOPES II 40 kg toe, terwijl 6 kg de maximaal toelaatbare massatraagheid is om ongehinderd te kunnen wandelen. Onderzoek van de looppatronen van gezonde proefpersonen laat zien dat het lopen in LOPES II in minimale impedantie modus, lijkt op vrij lopen op een loopband. Met name voor de gewrichtsrotaties zijn de correlaties hoog. Voor de bekken translaties zijn de correlaties lager, hetgeen ook blijkt uit de relatief hoge interactiekrachten op het bekken (piek-piek 100 N). Dit wordt toegeschreven aan de relatief hoge virtuele massa bij het bekken.

In de volgende fase hebben we een pilotstudie gedaan om het potentieel van LOPES II in de kliniek te evalueren. Voor patiënten die voor de eerste keer in LOPES II werden geïnstalleerd varieerde de donning time van 10 tot 15 minuten. Voor de tweede keer duurde het 5 tot 8 minuten. Bij patiënten die voor de eerste keer in LOPES II gingen trainen, moesten de lengtes van de ledematen worden opgemeten en in de computer ingevoerd worden. De donning time van zwaarder aangedane patiënten was langer, omdat zij moeilijk zelfstandig kunnen staan. Deze tijden zijn aanzienlijk korter dan de tijden voor bestaande apparaten, waardoor LOPES II efficiënter gebruikmaakt van de trainingstijd.

Tijdens de pilotstudies hebben we de mogelijkheden van Assist as Needed met LOPES II getest. Hiervoor hebben we een grafische gebruikersinterface ontwikkeld, waarmee de therapeut het looppatroon en de mate van ondersteuning voor de specifieke aspecten van het lopen kan aanpassen. LOPES II is krachtig en stijf genoeg om een looppatroon op een zwaar aangedane patiënt op te leggen (hoge ondersteuning op alle aspecten van het lopen). Aan de andere kant van het spectrum hebben we aangetoond dat LOPES II selectief kan ondersteunen bij mild aangedane patiënten.

LOPES II heeft de potentie om Assist as Needed looptraining naar de kliniek te brengen. Momenteel wordt een gerandomiseerde klinische studie uitgevoerd om het effect van training met LOPES II te vergelijken met conventionele therapie.

Revalidatiegeneeskunde

Advanced Insights in Upper Limb Function of Individuals with Cervical Spinal Cord Injury

Academisch Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Twente
op gezag van de Rector Magnificus
prof. dr. E. Brinksma
ten overstaan van een door het college voor promoties ingestelde
commissie, in het openbaar te verdedigen in de Agnietenkapel
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door

Inge-Marie Velstra

geboren op 1 mei 1967 te Apeldoorn

Promotor:	Prof.dr. J.S. Rietman Prof. dr. A. Curt
Copromotores:	Dr. M. Bolliger
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Samenvatting

Revalidatie heeft als doel om bij mensen met een gezondheidsprobleem het dagelijks functioneren te herstellen of te behouden. Bruikbare, betrouwbare en valide meetinstrumenten, die ook veranderingen in de gezondheidstoestand kunnen vastleggen, zijn nodig om binnen het revalidatieproces inzicht te krijgen in de onderliggende oorzaken van het verminderd functioneren.

Bij mensen met een cervicale dwarslaesie is de arm- en handfunctie aangedaan en daarom is de behandeling van de bovenste extremiteiten van groot belang. Er is echter beperkt onderzoek gedaan naar uitkomstmaten van arm- en handfunctie. Verder kan de uitingsvorm en het verloop van een cervicale dwarslaesie heel verschillend zijn, wat voornamelijk wordt bepaald door variatie in de hoogte, de ernst en het herstel van de laesie. Deze verschillen maken het lastig om de verschijnselen en testresultaten bij individuele patiënten te interpreteren en het bemoeilijkt ook de interpretatie van onderzoeksgegevens.

Hoofdstuk 1 van dit proefschrift laat zien dat er maar weinig meetinstrumenten voor mensen met een cervicale dwarslaesie zijn ontwikkeld en dat de meetinstrumenten die er wel zijn, geen, beperkte of matige klinimetrische meeteigenschappen bezitten. Om arm- en handfunctie nauwkeurig te kunnen weergeven is het daarom nodig om voor deze patiënten betrouwbare, valide en responsieve meetinstrumenten te ontwikkelen of om bij bestaande instrumenten de meeteigenschappen verder te onderzoeken. Het hoofddoel van dit proefschrift is om bij mensen met een cervicale dwarslaesie de arm- en handfunctie te meten, te evalueren en te voorspellen tot een jaar na het ontstaan van de laesie, middels de ‘Graded and Redefined Assessment of Strength, Sensibility and Prehension’ (GRASSP).

Hoofdstuk 2 beschrijft een systematische literatuurstudie naar de beschikbaarheid van meetinstrumenten voor arm- en handfunctie in vier verschillende patiëntengroepen: 1) aandoeningen van schouder-arm-hand; 2) reumatische ziekten; 3) herseninfarct; 4) tetraplegie. Met tetraplegie wordt een verlamming van zowel beide armen als beide benen bedoeld, zoals die kan ontstaan na een cervicale dwarslaesie. Er bleken 17 veelgebruikte meetinstrumenten te zijn, die volgens de ‘International Classification of Functioning, Disability, and Health’ (ICF) ingedeeld kunnen worden. Voor ieder meetinstrument is het onderliggend concept, de uit te voeren metingen en informatie over betrouwbaarheid en responsiviteit voor veranderingen gegeven. Samenvattend kan gezegd worden dat deze veelgebruikte meetinstrumenten onderling behoorlijke verschillen vertonen in concept en de metingen. Tevens mist er vaak informatie over de klinimetrische eigenschappen. Het overzicht (tabellen 2.1 en 2.2 in hoofdstuk 2) kan gebruikt worden om de keuze voor een meetinstrument in de klinische praktijk of voor een studie te vergemakkelijken.

Vanwege het gebrek aan goede meetinstrumenten voor de arm- en handfunctie voor mensen met een cervicale dwarslaesie, heeft een internationaal onderzoeksteam de ‘Graded and Redefined Assessment of Strength (spierkracht), Sensibility (tastzin) and Prehension (reiken, grijpen, loslaten en manipuleren)’ (GRASSP) ontwikkeld. De GRASSP is een meetinstrument dat veranderingen in functie van de arm en hand kan vastleggen, in relatie tot complexe vaardigheden

van de arm en hand. In **hoofdstuk 3** wordt een studie beschreven bij 74 patiënten met een acute cervicale dwarslaesie die op 1, 3, 6 en 12 maanden na de dwarslaesie zijn onderzocht. Onderzocht is of de GRASSP responsief is voor veranderingen over die tijd, in vergelijking met andere gestandaardiseerde tests (zoals de 'upper extremity motor score' (UEMS), de gevoeligheid voor lichte aanraking ('light touch', LT) die volgens internationale richtlijnen (ISNCSCI) getest worden en een schaal voor het niveau van zelfstandigheid bij activiteiten van de zelfverzorging (SCIMSS)). Verder is er gekeken naar het herstelpatroon van de onderdelen 'spierkracht' en 'prehension' in de GRASSP en is er gekeken in hoeverre veranderingen in de GRASSP en SCIM-SS overeenkwamen met veranderingen volgens het oordeel van behandelaars.

De GRASSP is uitstekend in staat is om tot een jaar na de dwarslaesie klinisch relevante veranderingen in arm- en handfunctie te meten. GRASSP spierkracht en prehension herstel waren het grootst tussen 1–3 maanden na het ontstaan van de dwarslaesie en zijn gerelateerd aan de ernst van de dwarslaesie. De metingen van de GRASSP bleken van toevoegende waarde te zijn bij de bestaande standaardmetingen (INSCSCI en SCIM-SS).

Bij mensen met een cervicale dwarslaesie treden niet alleen spierparesen op, maar bestaat er ook uitval van gevoel en tastzin. In **hoofdstuk 4** worden drie verschillende meetmethoden getest, die gebruikt worden om te onderzoeken wat mensen met een tetraplegie nog kunnen waarnemen met de huid van schouder arm en hand (op de dermatomen tussen C3-C8): de gevoeligheid voor lichte aanraking (LT), de Semmes-Weinstein monofilament (SWM) test en de grenswaarde om een elektrische prikkeling nog net waar te nemen (EPT). Bij 25 patiënten met tetraplegie zijn, 6 maanden na de laesie, in totaal 300 huidgebieden getest, zowel links als rechts.

Het percentage van overeenstemming tussen de LT en SWM/EPT testuitslagen varieerde van 95.5% tot 36.2%. De meetinstrumenten SWM en EPT zijn gevoeliger om tastzin te meten dan de LT, doordat er onder, boven en op het LT-niveau van de laesie nog tastzin met EPT en SWM gedetecteerd werd. Dat betekent dat SWM of EPT een goede aanvulling is op LT.

Er bestaat een grote variabiliteit in het verloop na het doormaken van een cervicale dwarslaesie. Voor de patiënt en voor de revalidatie zou het goed zijn als het verloop na de dwarslaesie zou kunnen worden voorspeld om daarmee de patiënten goed te informeren over hun vooruitgang. In **hoofdstuk 5** staat een studie beschreven, waarin onderzocht is of je met de GRASSP-test de arm- en handfunctie en de mate van zelfstandigheid bij zelfverzorging een jaar na de dwarslaesie kan voorspellen. In de studie is bij 61 patiënten 1 maand, 6 en 12 maanden na de dwarslaesie, de GRASSP, SCIM-SS en de American Spinal Injury Association (ASIA) Impairment Scale (AIS) (Gemodificeerde Frankel Classificatie om de mate van stoornis aan te geven) afgenomen. De spierkracht in de GRASSP bleek de beste voorspeller voor het verloop van arm- en handfunctie en zelfverzorging. De voorspelling werd nog beter als de spierkracht met het kwalitatieve grijpen en/of kwantitatieve grijpen werd gecombineerd. Kwalitatief grijpen werd getest met de 'qualitative grasping subtest'

(QlG) waarin verschillende grijppatronen zoals de cilindergreep, pincetgreep en lateraalgreep uitgevoerd worden *zonder* dat een voorwerp gepakt wordt. Kwantitatief grijpen werd getest met de 'quantitative grasping subtest' (QtG), waarin zes verschillende taken uitgevoerd worden, bijvoorbeeld water uit een flesje in een glas schenken en moeren op een boutje draaien, waarbij gekeken en beoordeeld wordt met welke greep de patiënt het voorwerp pakt. Bovendien leverde de beslisboomanalyse (decision tree analysis: URP-CTREE) belangrijke informatie op over de verdeling van verschillende homogene uitkomsten, zelfs uit een heterogene groep van patiënten waarvan het neurologische herstel zo verschillend is. In conclusie kan worden gesteld dat de GRASSP afgenomen op 1 maand na de dwarslaesie nauwkeurig het verloop van de armen handfunctie en zelfverzorging tot 1 jaar na de dwarslaesie kan voorspellen. Daarnaast laat de URP-CTREE-analyse zien dat de verdeling van uitkomsten uitstekend gebruikt kan worden om cohorten met homogene uitkomsten te voorspellen. Dit was tot nu toe erg moeilijk bij cervicale dwarslaesie en was nooit nader onderzocht. De bovengenoemde factoren ondersteunen het gebruik van de GRASSP in revalidatie en interventiestudies.

Uit de **hoofdstukken 3 en 5** is gebleken dat de GRASSP geschikt is om bij mensen met een acute cervicale dwarslaesie nauwkeurig herstelpatronen te beschrijven en om de arm- en handfunctie en zelfverzorging precies te voorspellen. De daaropvolgende vraag is in hoeverre de functie van individuele spieren of spiergroepen, zoals beschreven in de GRASSP en ISNCSCI-UEMS, samenhangt met latere arm- en handfunctie en zelfstandigheid in de zelfverzorging en mobiliteit. Ook was het nog de vraag in hoeverre QlG, zoals beschreven in de GRASSP en het motorische niveau van de laesie (MLI) en de ernst van de laesie (AIS), samenhangt met latere functionaliteit. In het onderzoek in **hoofdstuk 6** is beschreven dat een combinatie van maximaal vier verschillende spieren of spiergroepen predictoren uit ISNCSCI-UEMS en GRASSP de arm- en handfunctie 6 maanden later nauwkeurig kan voorspellen. Bovendien kan het testen van deze spieren heel bruikbaar zijn om te informeren over de juiste behandeling in de revalidatie. De QlG-predictoren leverden dezelfde resultaten op. Bij alle analyses werden de MLI- en AIS-predictoren niet in het model opgenomen. Dus een beperkt aantal spieren of spiergroepen alsook een eenvoudige en snelle test zoals QlG kunnen uitstekend de arm- en handfunctie voorspellen en patiënten in goede en slechte uitkomsten stratificeren onafhankelijk van MLI en AIS. Er kan geconcludeerd worden dat de voorspellende waarde van ISNCSCI-UEMS voor arm- en handfunctie significant verbeterd kan worden door GRASSP-predictoren toe te voegen.

In **hoofdstuk 7** worden de belangrijkste bevindingen van dit proefschrift gepresenteerd en besproken, en worden aanbevelingen gedaan voor verder onderzoek. Het werk in dit proefschrift geeft nieuw inzicht en waardevolle data over de arm- en handfunctie bij mensen met een cervicale dwarslaesie. De GRASSP is een relatief nieuwe test die informatie geeft over verschillende domeinen van arm- en handfunctie, zoals spierkracht, tastzin en de vaardigheid om naar voorwerpen te reiken, te grijpen, los te laten en te manipuleren. De GRASSP is in staat om de soms kleine maar klinisch belangrijke veranderingen in arm- en handfunctie te meten, die belangrijk zijn voor functieherstel. Met de uitslag van de GRASSP kan ook het verloop van arm- en handfunctie en zelfverzorging nauwkeurig voorspeld

worden, zelfs als bij cervicale dwarslaesie de gevolgen voor patiënten zo verschillend kunnen zijn. Dit ondersteunt het gebruik van de GRASSP voor het meten van de uitkomsten in de revalidatie van mensen met een cervicale dwarslaesie en ondersteunt tevens het gebruik van de GRASSP in klinische studies.

PubMed publicaties per vakgroep
Anesthesiologie

1. Intraoperative High-Dose Dexamethasone and Severe AKI after Cardiac Surgery
Jacob KA, Leaf DE, Dieleman JM, van Dijk D, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, de Lange F, Boer C, Kluin J, Waikar SS

Administration of prophylactic glucocorticoids has been suggested as a strategy to reduce postoperative AKI and other adverse events after cardiac surgery requiring cardiopulmonary bypass. In this post hoc analysis of a large placebo-controlled randomized trial of dexamethasone in 4465 adult patients undergoing cardiac surgery, we examined severe AKI, defined as use of RRT, as a primary outcome. Secondary outcomes were doubling of serum creatinine level or AKI-RRT, as well as AKI-RRT or in-hospital mortality (RRT/death). The primary outcome occurred in ten patients (0.4%) in the dexamethasone group and in 23 patients (1.0%) in the placebo group (relative risk, 0.44; 95% confidence interval, 0.19 to 0.96). In stratified analyses, the strongest signal for potential benefit of dexamethasone was in patients with an eGFR<15 ml/min per 1.73 m^2. In conclusion, compared with placebo, intraoperative dexamethasone appeared to reduce the incidence of severe AKI after cardiac surgery in those with advanced CKD.

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Impact factor: 9.343

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2. Intraoperative High-Dose Dexamethasone in Cardiac Surgery and the Risk of Rethoracotomy
van Osch D, Dieleman JM, Nathoe HM, Boasson MP, Kluin J, Bunge JJ, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, de Lange F, Boer C, van Dijk D

Background: Cardiac surgery with the use of cardiopulmonary bypass is associated with a systemic inflammatory response. Intraoperative corticosteroids are administered to attenuate this inflammatory response. The recent Dexamethasone for Cardiac Surgery (DECS) trial could not demonstrate a beneficial effect of dexamethasone on major adverse events in cardiac surgical patients. Previous studies suggest that corticosteroids may affect postoperative coagulation and blood loss, and therefore could influence the risk of surgical reinterventions. We investigated the effects of prophylactic intraoperative dexamethasone treatment on the rate of rethoracotomy after cardiac surgery.
Methods: We performed a post-hoc additional data collection and analysis in the DECS trial. A total of 4,494 adult patients undergoing cardiac surgery with cardiopulmonary bypass were randomly assigned to intravenous dexamethasone (1.0 mg/kg) or placebo. The primary endpoint for the present study was the incidence of any rethoracotomy within the first 30 postoperative days. Secondary

endpoints included the reason for rethoracotomy and the incidence of perioperative transfusion of blood products.
Results: In the dexamethasone group, 217 patients (9.7%) underwent a rethoracotomy, and in the placebo group, 165 patients did (7.3%; relative risk 1.32, 95% confidence interval: 1.09 to 1.61, p = 0.005). The most common reason for rethoracotomy was tamponade in both groups: 3.9% versus 2.1%, respectively (relative risk 1.84, 95% confidence interval: 1.30 to 2.61, p < 0.001).
Conclusions: Intraoperative high-dose dexamethasone administration in cardiac surgery was associated with an increased rethoracotomy risk.

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Impact factor: 3.849

Totale impact factor: 13.192
Gemiddelde impact factor: 6.596

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

Automatisering

1. The organizational and clinical impact of integrating bedside equipment to an information system: a systematic literature review of patient data management systems (PDMS)
Cheung A, van Velden FH, Lagerburg V, Minderman N

Objective: The introduction of an information system integrated to bedside equipment requires significant financial and resource investment; therefore understanding the potential impact is beneficial for decision-makers. However, no systematic literature reviews (SLRs) focus on this topic. This SLR aims to gather evidence on the impact of the aforementioned system, also known as a patient data management system (PDMS) on both organizational and clinical outcomes.
Materials and Methods: A literature search was performed using the databases Medline/PubMed and CINHAL for English articles published between January 2000 and December 2012. A quality assessment was performed on articles deemed relevant for the SLR.
Results: Eighteen articles were included in the SLR. Sixteen articles investigated the impact of a PDMS on the organizational outcomes, comprising descriptive, quantitative and qualitative studies. A PDMS was found to reduce the charting time, increase the time spent on direct patient care and reduce the occurrence of errors. Only two articles investigated the clinical impact of a PDMS. Both reported an improvement in clinical outcomes when a PDMS was integrated with a clinical decision support system (CDSS).
Conclusions: A PDMS has shown to offer many advantages in both the efficiency and the quality of care delivered to the patient. In addition, a PDMS integrated to a CDSS may improve clinical outcomes, although further studies are required for validation.

Gepubliceerd: Int J Med Inform 2015;84(3):155-65
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Totale impact factor: 2.004
Gemiddelde impact factor: 2.004

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 2.004
Gemiddelde impact factor: 2.004

Cardiologie

1. Presence of albuminuria predicts left ventricular mass in patients with chronic systemic arterial hypertension
de Beus E, Meijs MF, Bots ML, Visseren FL, Blankestijn PJ

Background: Increased left ventricular mass (LVM) is known to predict cardiovascular morbidity and mortality. LVM is high in patients with advanced kidney disease. Our aim was to study the relationship between renal parameters and LVM in hypertensive subjects at high risk of cardiovascular disease.
Design: Cardiac MRI was performed in 527 patients participating in the single-centre SMART cohort study. Participants free from previous symptomatic coronary heart disease but with a history of hypertension were recruited. Subjects were screened for cardiovascular risk factors in a standardized way. Multivariable linear regression was used to study the relationship of both estimated glomerular filtration rate (eGFR) and presence of albuminuria with left ventricular mass.
Results: Mean LVM was 121 g for men (SD 26) and 87 g for women (SD 20). Mean eGFR was 82 mL/min/1.73 m((2)) (SD 19). A total of 73 patients (14%) had albuminuria. After adjusting for known determinants of LVM (height, weight, sex and age) eGFR did not relate to LVM while presence of albuminuria did (mean change in LVM per 10 mL/min/1.73 m(2) change in eGFR 0.79 g, 95% CI -0.33 to 1.91, P = 0.17, mean change in LVM in presence vs. absence of albuminuria 9.9 g, 95% CI 4.33 to 15.45, P = 0.001). Additional adjustment for systolic blood pressure did not change results (B for eGFR 0.54, 95% CI -0.58 to 1.66, P = 0.35, B for albuminuria 9.09, 95% CI 3.57 to 14.60, P = 0.001).
Conclusions: In this study in hypertensive patients with high vascular risk, albuminuria was related to increased LVM and eGFR was not.

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Impact factor: 2.734

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2. Changes in ischaemia as assessed with single-photon emission computed tomography myocardial perfusion imaging in high-risk patients with diabetes without cardiac symptoms: relation with coronary atherosclerosis on computed tomography coronary angiography
de Graaf MA, Roos CJ, Mansveld JM, Kharagjitsingh AV, Dibbets-Schneider P, Kroft LJ, Jukema JW, Ficaro EP, Bax JJ, Scholte AJ

Aims: The study aims (i) to evaluate changes in myocardial ischaemia on single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) after 2 years in a cohort of high-risk patients with diabetes without cardiac symptoms or known coronary artery disease (CAD) and (ii) to assess the value of baseline computed tomography coronary angiography (CTA)-derived coronary atherosclerosis parameters to predict changes in myocardial ischaemia.
Methods and Results: The population consisted of 100 high-risk patients with diabetes without cardiac symptoms referred for cardiovascular risk stratification. All

patients underwent coronary artery calcium (CAC) scoring, CTA, and SPECT MPI. After 2 years of follow-up, SPECT MPI was repeated to evaluate potential progression of ischaemia.In total, 20% of patients presented with ischaemia at baseline. Of these 20 patients, 7 (35%) still had ischaemia at follow-up, whereas 13 (65%) showed resolution and 4 (20%) showed progression of ischaemia at follow-up. Of the 80 patients without ischaemia at baseline, 65 (81%) had a normal MPI at follow-up and 15 patients (19%) presented with new ischaemia. There were no significant differences in the CAC score or the extent, severity, and composition of CAD on CTA between patients with and without ischaemia at baseline. Similarly, no differences could be demonstrated between patients with and without ischaemia at follow-up or between patients with and without progression of ischaemia.
Conclusion: The rate of progression of ischaemia in high-risk patients with diabetes without cardiac symptoms is limited. Few patients presented with new ischaemia, whereas some patients showed resolution of ischaemia. Atherosclerosis parameters on CTA were not predictive of new-onset ischaemia or progression of ischaemia.

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3. Long-term results of surgical minimally invasive pulmonary vein isolation for paroxysmal lone atrial fibrillation
De Maat GE, Pozzoli A, Scholten MF, Van Gelder IC, Blaauw Y, Mulder BA, Bella PD, Alfieri OR, Benussi S, Mariani MA

Aims: Transcatheter pulmonary vein ablation is the current treatment of choice for symptomatic drug-refractory atrial fibrillation (AF). Video-assisted surgical pulmonary vein isolation (sPVI) is an alternative therapy to percutaneous ablation for the treatment of AF. Long-term results of sPVI are currently unknown. The aim of this study was to report on the long-term efficacy and safety of sPVI in patients with paroxysmal AF.
Methods and Results: The study design was observational and retrospective. From July 2005 to January 2011, 42 patients with drug-refractory paroxysmal AF underwent video-assisted sPVI in two different centres. Patients were eligible for sPVI when suffering from symptomatic, drug-refractory paroxysmal AF and they agreed to the alternative of sPVI. The median preoperative AF duration was 24 months (range 3-200). Success was defined as the absence of AF on 24 h or 96 h Holter monitoring during follow-up, off antiarrhythmic drugs (AAD). Adverse events and follow-up monitoring were based on the Heart Rhythm Society Consensus Statement 2012 for the catheter and surgical ablation of AF. Mean age was 55 +/- 10 years, and 76% were males. After a mean follow-up of 5 years (SD 1.7), 69% of all patients were free from atrial arrhythmias without the use of AAD, and 83% with the use of AAD. Major peri-procedural adverse events occurred in four (9.5%) patients, no strokes or mortalities were registered during long-term follow-up.
Conclusion: This retrospective study shows that sPVI for the treatment of paroxysmal AF is effective and that the outcomes are maintained at long-term follow-up.

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Impact factor: 3.670

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4. Reassessing noninducibility as ablation endpoint of post-infarction ventricular tachycardia: the impact of left ventricular function
de Riva Silva M, Piers SR, Kapel GF, Watanabe M, Venlet J, Trines SA, Schalij MJ, Zeppenfeld K

Background: Noninducibility is frequently used as procedural end point of ventricular tachycardia (VT) ablation after myocardial infarction. We investigated the influence of left ventricular (LV) function on the predictive value of noninducibility for VT recurrence and cardiac mortality.
Methods and Results: Ninety-one patients (82 men, 67+/-10 years) with post-myocardial infarction VT underwent ablation between 2009 and 2012. Fifty-nine (65%) had an LV ejection fraction (EF) >30% (mean 41+/-7) and 32 (35%) an LVEF</=30% (mean 20+/-5). Thirty patients (51%) with EF>30% and 13 (41%) with EF</=30% were noninducible after ablation (P=0.386). During a median follow-up of 23 (Q1-Q3 16-36) months, 35 patients (38%) experienced VT recurrences and 17 (18%) cardiac death. At 1 year follow-up, survival free from VT recurrence and cardiac death for patients with LVEF>30% was 80% (95% confidence interval [CI], 70-90) compared with 42% (95% CI, 33-51) for those with LVEF</=30% (P=0.001). Noninducible patients with LVEF>30% had a recurrence-free survival from cardiac death of 90% (95% CI, 71-100) compared with 65% (95% CI, 47-83) for inducible patients (P=0.015). In the subgroup of patients with LVEF</=30%, the survival free from VT recurrence and cardiac death was 31% (95% CI, 0%-60%) for noninducible compared with 39% (95% CI, 27-52) for those who remained inducible (P=0.842).
Conclusions: Noninducible patients with moderately depressed LV function have a favorable outcome compared with patients who remained inducible after ablation. On the contrary, patients with severely depressed LV function have a poor prognosis independent of the acute procedural outcome.

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Impact factor: 4.678

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5. Author reply
Dorman HG, Scholten MF, Stevenhagen J, Van Opstal JM

Gepubliceerd: Europace 2015;17(1):166-7
Impact factor: 3.670

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6. Use of a biventricular implantable cardioverter defibrillator in a patient with a neurostimulator: is it a safe combination?
Dorman HG, Onrust A, Brants R, Stevenhagen YJ, Scholten MF

Gepubliceerd: Neth Heart J 2015 Feb;23(2):145-6
Impact factor: 1.837

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7. Prospective Assessment of the Diagnostic Accuracy of Instantaneous Wave-Free Ratio to Assess Coronary Stenosis Relevance: Results of ADVISE II International, Multicenter Study (ADenosine Vasodilator Independent Stenosis Evaluation II)

Escaned J, Echavarria-Pinto M, Garcia-Garcia HM, van de Hoef TP, de Vries T, Kaul P, Raveendran G, Altman JD, Kurz HI, Brechtken J, Tulli M, von Birgelen C, Schneider JE, Khashaba AA, Jeremias A, Baucum J, Moreno R, Meuwissen M, Mishkel G, van Geuns RJ, Levite H, Lopez-Palop R, Mayhew M, Serruys PW, Samady H, Piek JJ, Lerman A

Objectives: The purpose of this study was to assess the diagnostic accuracy of the instantaneous wave-free ratio (iFR) to characterize, outside of a pre-specified range of values, stenosis severity, as defined by fractional flow reserve (FFR) </=0.80, in a prospective, independent, controlled, core laboratory-based environment.
Background: Studies with methodological heterogeneity have reported some discrepancies in the classification agreement between iFR and FFR. The ADVISE II (ADenosine Vasodilator Independent Stenosis Evaluation II) study was designed to overcome limitations of previous iFR versus FFR comparisons.
Methods: A total of 919 intermediate coronary stenoses were investigated during baseline and hyperemia. From these, 690 pressure recordings (n = 598 patients) met core laboratory physiology criteria and are included in this report.
Results: The pre-specified iFR cut-off of 0.89 was optimal for the study and correctly classified 82.5% of the stenoses, with a sensitivity of 73.0% and specificity of 87.8% (C statistic: 0.90 [95% confidence interval (CI): 0.88 to 0.92, p < 0.001]). The proportion of stenoses properly classified by iFR outside of the pre-specified treatment (</=0.85) and deferral (>/=0.94) values was 91.6% (95% CI: 88.8% to 93.9%). When combined with FFR use within these cut-offs, the percent of stenoses properly classified by such a pre-specified hybrid iFR-FFR approach was 94.2% (95% CI: 92.2% to 95.8%). The hybrid iFR-FFR approach obviated vasodilators from 65.1% (95% CI: 61.1% to 68.9%) of patients and 69.1% (95% CI: 65.5% to 72.6%) of stenoses.
Conclusions: The ADVISE II study supports, on the basis rigorous methodology, the diagnostic value of iFR in establishing the functional significance of coronary stenoses, and highlights its complementariness with FFR when used in a hybrid iFR-FFR approach. (ADenosine Vasodilator Independent Stenosis Evaluation II-ADVISE II; NCT01740895).

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Impact factor: 7.345

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8. Impact of Clinical Presentation (Stable Angina Pectoris vs Unstable Angina Pectoris or Non-ST-Elevation Myocardial Infarction vs ST-Elevation Myocardial

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

The long-term risk associated with different coronary artery disease (CAD) presentations in women undergoing percutaneous coronary intervention (PCI) with drug-eluting stents (DES) is poorly characterized. We pooled patient-level data for women enrolled in 26 randomized clinical trials. Of 11,577 women included in the pooled database, 10,133 with known clinical presentation received a DES. Of them, 5,760 (57%) had stable angina pectoris (SAP), 3,594 (35%) had unstable angina pectoris (UAP) or non-ST-segment-elevation myocardial infarction (NSTEMI), and 779 (8%) had ST-segment-elevation myocardial infarction (STEMI) as clinical presentation. A stepwise increase in 3-year crude cumulative mortality was observed in the transition from SAP to STEMI (4.9% vs 6.1% vs 9.4%; p <0.01). Conversely, no differences in crude mortality rates were observed between 1 and 3 years across clinical presentations. After multivariable adjustment, STEMI was independently associated with greater risk of 3-year mortality (hazard ratio [HR] 3.45; 95% confidence interval [CI] 1.99 to 5.98; p <0.01), whereas no differences were observed between UAP or NSTEMI and SAP (HR 0.99; 95% CI 0.73 to 1.34; p = 0.94). In women with ACS, use of new-generation DES was associated with reduced risk of major adverse cardiac events (HR 0.58; 95% CI 0.34 to 0.98). The magnitude and direction of the effect with new-generation DES was uniform between women with or without ACS (pinteraction = 0.66). In conclusion, in women across the clinical spectrum of CAD, STEMI was associated with a greater risk of long-term mortality. Conversely, the adjusted risk of mortality between UAP or NSTEMI and SAP was similar. New-generation DESs provide improved long-term clinical outcomes irrespective of the clinical presentation in women.

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Impact factor: 3.276

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9. Cardiac function and cardiac events 1-year postpartum in women with congenital heart disease
Kampman MA, Balci A, Groen H, van Dijk AP, Roos-Hesselink JW, van Melle JP, Sollie-Szarynska KM, Wajon EM, Mulder BJ, van Veldhuisen DJ, Pieper PG

Background: Pregnancy is increasingly common in women with congenital heart disease (CHD), but little is known about long-term cardiovascular outcome after pregnancy in these patients. We studied the incidence of cardiovascular events 1-year postpartum and compared cardiac function prepregnancy and 1-year postpartum in women with CHD.
Methods: From our national, prospective multicenter cohort study, 172 women were studied. Follow-up with clinical evaluation and echocardiography and NT-proBNP

measurement were performed during pregnancy and 12 months postpartum. Cardiovascular events were defined as need for an urgent invasive cardiovascular procedure, heart failure, arrhythmia, thromboembolic events, myocardial infarction, cardiac arrest, cardiac death, endocarditis, and aortic dissection.
Results: Cardiovascular events were observed after 11 pregnancies (6.4%). Women with cardiovascular events postpartum had significant higher NT-proBNP values at 20-week gestation (191 [137-288] vs 102.5 [57-167]; P = .049) and 1-year postpartum compared with women without cardiovascular events postpartum (306 [129-592] vs 105 [54-187] pg/mL; P = .014). Women with cardiovascular events during pregnancy were at higher risk for late cardiovascular events (HR 7.1; 95% CI 2.0-25.3; P = .003). In women with cardiovascular events during pregnancy, subpulmonary end-diastolic diameter had significantly increased 1-year postpartum (39.0 [36.0-48.0] to 44.0 [40.0-50.0]; P = .028). No other significant differences were found in cardiac function or size 1-year postpartum compared with preconception values.
Conclusions: Cardiovascular events are relatively rare 1 year after pregnancy in women with CHD. Women with cardiovascular events during pregnancy are prone to develop cardiovascular events 1-year postpartum and have increased subpulmonary ventricular diameter compared with preconception values.

Gepubliceerd: Am Heart J 2015 Feb;169(2):298-304
Impact factor: 4.463

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10. Re-entry using anatomically determined isthmuses: a curable ventricular tachycardia in repaired congenital heart disease
Kapel GF, Reichlin T, Wijnmaalen AP, Piers SR, Holman ER, Tedrow UB, Schalij MJ, Stevenson WG, Zeppenfeld K

Background: Ventricular tachycardia (VT) is an important cause of late morbidity and mortality in repaired congenital heart disease. The substrate often includes anatomic isthmuses that can be transected by radiofrequency catheter ablation similar to isthmus block for atrial flutter. This study evaluates the long-term efficacy of isthmus block for treatment of re-entry VT in adults with repaired congenital heart disease.
Methods and Results: Thirty-four patients (49+/-13 years; 74% male) with repaired congenital heart disease who underwent radiofrequency catheter ablation of VT in 2 centers were included. Twenty-two (65%) had a preserved left and right ventricular function. Patients were inducible for 1 (interquartile range, 1-2) VT, median cycle length: 295 ms (interquartile range, 242-346). Ablation aimed to transect anatomic isthmuses containing VT re-entry circuit isthmuses. Procedural success was defined as noninducibility of any VT and transection of the anatomic isthmus and was achieved in 25 (74%) patients. During long-term follow-up (46+/-29 months), all patients with procedural success (18/25 with internal cardiac defibrillators) were free of VT recurrence but 7 of 18 experienced internal cardiac defibrillator-related complications. One patient with procedural success and depressed cardiac function received an internal cardiac defibrillator shock for ventricular fibrillation. None of the 18 patients (12/18 with internal cardiac defibrillators) with complete success and

preserved cardiac function experienced any ventricular arrhythmia. In contrast, VT recurred in 4 of 9 patients without procedural success. Four patients died from nonarrhythmic causes.
Conclusions: In patients with repaired congenital heart disease with preserved ventricular function and isthmus-dependent re-entry, VT isthmus ablation can be curative.

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Impact factor: 4.678

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11. Patient preference regarding assessment of clinical follow-up after percutaneous coronary intervention: the PAPAYA study
Kok MM, von Birgelen C, Lam MK, Lowik MM, van Houwelingen KG, Stoel MG, Louwerenburg JH, de Man FH, Hartmann M, Doggen CJ, van Til JA, IJzerman MJ

Aims: To keep patients in long-term clinical follow-up programmes after percutaneous coronary intervention (PCI), knowledge of the patient-preferred mode for follow-up assessment is crucial. We systematically assessed patient preference, and explored potential relationships with age and gender.
Methods and Results: In the prospective, observational PAPAYA study, 2,566 patients, treated by PCI between June 2008 and May 2012, were invited to participate in a postal survey on the patient-preferred mode (postal questionnaire, telephone or e-mail consultation) and frequency of follow-up assessment. A total of 1,797 (70.0%) patients responded. The vast majority preferred completing postal questionnaires (1,248 [69.9%]) as compared to telephone (240 [13.4%]) or e-mail-based approaches (227 [12.7%]) ($p<0.001$). With increasing age, there was a gradual decline in preference for e-mail ($p<0.001$); the youngest patients (</=60 years) preferred e-mail-based follow-up more often than the oldest (21.1% vs. 3.1%). Nevertheless, 79.9% of the youngest preferred to be approached in ways other than by e-mail. Women more often preferred approaches other than e-mail (94.1% vs. 87.3%, $p<0.001$).
Conclusions: Patients showed a distinct preference for completing postal questionnaires rather than being approached by telephone or e-mail. Younger patients accepted e-mail-based follow-up more often, but the majority of the youngest patients still preferred approaches other than by e-mail.

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Impact factor: 3.769

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12. Secundum atrial septal defect is associated with reduced survival in adult men
Kuijpers JM, van der Bom T, van Riel AC, Meijboom FJ, van Dijk AP, Pieper PG, Vliegen HW, Waskowsky WM, Oomen T, Zomer AC, Wagenaar LJ, Heesen WF, Roos-Hesselink JW, Zwinderman AH, Mulder BJ, Bouma BJ

Aims: The identification of sex differences in the prognosis of adults with a secundum atrial septal defect (ASD2) could help tailor their clinical management, as it has in other cardiovascular diseases. We investigated whether disparity between the sexes exists in long-term outcome of adult ASD2 patients.
Methods and Results: Patients with ASD2 classified as the primary defect were selected from the Dutch national registry of adult congenital heart disease. Survival stratified by sex was compared with a sex-matched general population. In a total of 2207 adult patients (mean age at inclusion 44.8 years, 33.0% male), 102 deaths occurred during a cumulative follow-up of 13 584 patient-years. Median survival was 79.7 years for men and 85.6 years for women with ASD2. Compared with the age- and sex-matched general population, survival was lower for male, but equal for female patients (P = 0.015 and 0.766, respectively). Logistic regression analyses showed that men had a higher risk of conduction disturbances (OR = 1.63; 95% CI, 1.22-2.17) supraventricular dysrhythmias (OR = 1.41; 1.12-1.77), cerebrovascular thromboembolic events (OR = 1.53; 1.10-2.12), and heart failure (OR = 1.91; 1.06-3.43).
Conclusion: In contrast to women, adult men with an ASD2 have worse survival than a sex-matched general population. Male patients also have a greater risk of morbidity during adult life. Sex disparity in survival and morbidity suggests the need for a sex-specific clinical approach towards these patients.

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Impact factor: 15.203

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13. Clinical Outcome of Patients With Implantation of Second-Generation Drug-Eluting Stents in the Right Coronary Ostium: Insights from 2-Year Follow-up of the TWENTE Trial
Lam MK, Sen H, Tandjung K, Lowik MM, Basalus MW, Mewes JC, Stoel MG, van Houwelingen KG, Linssen GC, IJzerman MJ, Doggen CJ, von Birgelen C

Objectives: The aim of the present study was to assess the impact on clinical outcome of RCA ostial coverage with second-generation DES. Background: Treatment of the aorta-ostial (AO) region of the right coronary artery (RCA) with bare metal stents and first-generation drug-eluting stents (DES) has been associated with a higher risk of target-lesion revascularisation (TLR).
Methods: Of the 1,391 patients of the prospective TWENTE trial, we identified 321 (23%) with single-vessel RCA treatment, who were categorized into stenting with AO coverage (AOC) versus stenting without AOC. The AO region was defined as 3 mm from the aortic orifice.
Results: The 67 (20.9%) patients with AOC showed more severe lesion calcifications than the 254 patients without AOC (31.3% vs. 12.6%; p<0.01). In the AOC group, there was a higher prevalence of hypercholesterolemia and family history of coronary disease (75.4% vs. 61.6%, and 68.7% vs. 53.5%, respectively; p=0.03). During 2-year follow-up, patients in the AOC group had a higher incidence of TLR (7.5% vs. 1.6%; p=0.02). Following adjustment for confounders, AOC independently predicted TLR with an adjusted hazzard ratio of 4.1 (95%CI: 1.17-14.39; p=0.03).

Conclusion: AO treatment of the RCA with second-generation DES is feasible, but our data suggest that stent coverage of the right aorta-ostial segment remains a predictor of TLR.

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Impact factor: 2.107

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14. Coronary artery dominance and the risk of adverse clinical events following percutaneous coronary intervention: insights from the prospective, randomised TWENTE trial
Lam MK, Tandjung K, Sen H, Basalus MW, van Houwelingen KG, Stoel MG, Louwerenburg JW, Linssen GC, Said SA, Nienhuis MB, de Man FH, van der Palen J, von Birgelen C

Aims: To investigate the prognostic value of coronary dominance for various adverse clinical events following the implantation of drug-eluting stents.
Methods and results: We assessed two-year follow-up data of 1,387 patients from the randomised TWENTE trial. Based on the origin of the posterior descending coronary artery, coronary circulation was categorised into left and non-left dominance (i.e., right and balanced). Target vessel-related myocardial infarction (MI) was defined according to the updated Academic Research Consortium (ARC) definition (2x upper reference limit of creatine kinase [CK], confirmed by CK-MB elevation), and periprocedural MI (PMI) as MI </=48 hours following PCI. One hundred and thirty-six patients (9.8%) had left and 1,251 (90.2%) non-left dominance. Target lesions were more frequently located in dominant arteries (p<0.005). Left dominance was associated with more severe calcifications (p=0.006) and more bifurcation lesions (p=0.031). Non-left dominance tended to be less frequent in men (p=0.09). Left coronary dominance was associated with more target vessel-related MI (14 [10.3%] vs. 62 [5.0%], p=0.009). Left dominance independently predicted PMI (adjusted HR 2.19, 95% CI: 1.15-4.15, p=0.017), while no difference in other clinical endpoints was observed between dominance groups.
Conclusions: In the population of the TWENTE trial, we observed a higher incidence of periprocedural myocardial infarction in patients who had left coronary dominance.

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Impact factor: 3.769

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15. Three-year clinical outcome of patients with bifurcation treatment with second-generation Resolute and Xience V stents in the randomized TWENTE trial
Lam MK, Sen H, van Houwelingen KG, Lowik MM, van der Heijden LC, Kok MM, de Man FH, Linssen GC, Tandjung K, Doggen CJ, von Birgelen C

Background: Only limited data from large randomized clinical trials have been published on the long-term performance of second-generation drug-eluting stents in bifurcation lesions.
Methods: We investigated in patients in the randomized TWENTE trial the long-term safety and efficacy of treating bifurcation lesions with 2 widely applied second-generation drug-eluting stents, the zotarolimus-eluting Resolute stent (Medtronic Inc, Santa Rosa, CA) and the everolimus-eluting Xience V stent (Abbott Vascular, Santa Clara, CA). Three-year follow-up was available in 99.3%. Patients were categorized into treatment for >/=1 bifurcation lesion versus treatment for nonbifurcation lesions only.
Results: Among the 1,391 patients of the TWENTE trial, 362 (26%) were treated for bifurcation lesions. At 3-year follow-up, target-vessel failure did not differ between patients treated for bifurcation versus nonbifurcation lesions (13.1% vs 12.6%; P = .84), whereas the periprocedural myocardial infarction rate was higher in patients with bifurcation lesions (6.9% vs 3.1%; P < .01). Of the 362 patients with bifurcation lesion treatment, 179 (49.4%) were treated with Resolute and 183 (50.6%) with Xience V. There was no significant difference in target-vessel failure between the Resolute and Xience V groups with bifurcation treatment (13.6% vs 12.6%; P = .78), and their incidence of definite-or-probable stent thrombosis was low and similar (1.1% vs 0.5%, respectively; P = .62).
Conclusion: Despite a significant difference in periprocedural myocardial infarction, 3-year clinical outcome after implantation of second-generation stents was favorable and similar for patients with and without bifurcation lesions. In addition, we observed no difference in long-term clinical outcome after bifurcation lesion treatment with Resolute and Xience V stents.

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Impact factor: 4.463

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16. Safety of second-generation drug-eluting stents three years after randomised use in the TWENTE trial
Lowik MM, Lam MK, Sen H, Tandjung K, van Houwelingen KG, de Man FH, Stoel MG, Louwerenburg JH, Linssen GC, Doggen CJ, von Birgelen C

Aims: To assess three-year clinical outcome following randomised use of the second-generation Resolute zotarolimus-eluting stent (ZES) and the XIENCE V everolimus-eluting stent (EES). For Resolute ZES and randomised use, outcome data >/=3 years are relatively scarce.
Methods and Results: The TWENTE trial examined 1,391 patients with stable angina or non-ST-elevation acute coronary syndromes, of whom 21.6% were diabetics, 70.1% had complex B2 or C lesions and 77.4% had "off-label" indications for DES use. Three-year follow-up data were obtained in 1,381 patients (99.3%; 10 withdrawals). Adverse clinical events were independently adjudicated. The primary endpoint target vessel failure (TVF), a composite of cardiac death, target vessel-related myocardial infarction and clinically indicated target vessel revascularisation, was 12.1% for Resolute ZES and 13.4% for XIENCE V EES (p=0.50). Cardiac death rates were 1.9% vs. 3.5% (p=0.06); the other individual components of TVF also

showed no significant between-group differences. The rates of definite-or-probable stent thrombosis (1.4% vs. 1.6%, p=0.82) and very late stent thrombosis (0.6% vs. 0.4%, p=1.0) did not differ between the groups.
Conclusions: Three-year follow-up data of patients included in the randomised TWENTE trial demonstrated similar and sustained safety and efficacy of Resolute ZES and XIENCE V EES.

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Impact factor: 3.769

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17. Endocarditis of bovine Contegra valved conduit: a PET-CT spot diagnosis
Mauritz GJ, Wagenaar L, van der Jagt L, Bouman D

Gepubliceerd: Eur Heart J Cardiovasc Imaging 2015 Jun 14;16(10):1173
Impact factor: 4.105

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18. Diagnostic yield of external loop recording in patients with acute ischemic stroke or TIA
Plas GJ, Bos J, Oude Velthuis B, Scholten MF, den Hertog HM, Brouwers PJ

Atrial fibrillation (AF) is a strong risk factor for first-ever stroke and stroke recurrence. The detection rate is low and detection is often costly and time-consuming. We evaluated the diagnostic yield of an external loop recorder (ELR) in patients with acute ischemic stroke or TIA, and assessed factors that are associated with AF detection. We prospectively studied patients admitted to the stroke unit with ischemic stroke or TIA, without a history of AF, and no AF on routine-ECG and 24-h telemetry. Patients received an ELR for another 24-h registration. Rhythm registration with an ELR was performed in 94 patients. AF was identified in 5 patients (5 %). AF was associated with cryptogenic stroke and cortical or subcortical involvement. If ELR was limited to patients with cryptogenic stroke in combination with cortical or subcortical involvement, the detection rate increased to 17 %. Automated recording with ELR was easy to use in the acute setting of ischemic stroke or TIA and seems promising to detect AF or atrial flutter, in particular in patients with cryptogenic stroke in combination with cortical or subcortical symptoms.

Gepubliceerd: J Neurol 2015 Mar;262(3):682-8
Impact factor: 3.377

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19. Safety of Prasugrel Loading Doses in Patients Pre-Loaded With Clopidogrel in the Setting of Primary Percutaneous Coronary Intervention: Results of a Nonrandomized Observational Study
Räber L, Klingenberg R, Heg D, Kelbaek H, Roffi M, Tuller D, Baumbach A, Zanchin T, Carballo D, Ostojic M, Stefanini GG, Rodondi N, von Birgelen C, Moschovitis A,

Engstrom T, Gencer B, Auer R, Meier B, Mach F, Luscher TF, Juni P, Matter CM, Windecker S

Objectives: The aim of this study was to assess the safety of the concurrent administration of a clopidogrel and prasugrel loading dose in patients undergoing primary percutaneous coronary intervention.
Background: Prasugrel is one of the preferred P2Y12 platelet receptor antagonists for ST-segment elevation myocardial infarction patients. The use of prasugrel was evaluated clinically in clopidogrel-naive patients.
Methods: Between September 2009 and October 2012, a total of 2,023 STEMI patients were enrolled in the COMFORTABLE (Comparison of Biomatrix Versus Gazelle in ST-Elevation Myocardial Infarction [STEMI]) and the SPUM-ACS (Inflammation and Acute Coronary Syndromes) studies. Patients receiving a prasugrel loading dose were divided into 2 groups: 1) clopidogrel and a subsequent prasugrel loading dose; and 2) a prasugrel loading dose. The primary safety endpoint was Bleeding Academic Research Consortium types 3 to 5 bleeding in hospital at 30 days.
Results: Of 2,023 patients undergoing primary percutaneous coronary intervention, 427 (21.1%) received clopidogrel and a subsequent prasugrel loading dose, 447 (22.1%) received a prasugrel loading dose alone, and the remaining received clopidogrel only. At 30 days, the primary safety endpoint was observed in 1.9% of those receiving clopidogrel and a subsequent prasugrel loading dose and 3.4% of those receiving a prasugrel loading dose alone (adjusted hazard ratio [HR]: 0.57; 95% confidence interval [CI]: 0.25 to 1.30, p = 0.18). The HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) bleeding score tended to be higher in prasugrel-treated patients (p = 0.076). The primary safety endpoint results, however, remained unchanged after adjustment for these differences (clopidogrel and a subsequent prasugrel loading dose vs. prasugrel only; HR: 0.54 [95% CI: 0.23 to 1.27], p = 0.16). No differences in the composite of cardiac death, myocardial infarction, or stroke were observed at 30 days (adjusted HR: 0.66, 95% CI: 0.27 to 1.62, p = 0.36).
Conclusions: This observational, nonrandomized study of ST-segment elevation myocardial infarction patients suggests that the administration of a loading dose of prasugrel in patients pre-treated with a loading dose of clopidogrel is not associated with an excess of major bleeding events. (Comparison of Biomatrix Versus Gazelle in ST-Elevation Myocardial Infarction [STEMI] [COMFORTABLE]; NCT00962416; and Inflammation and Acute Coronary Syndromes [SPUM-ACS]; NCT01000701).

Gepubliceerd: JACC Cardiovasc Interv 2015 Jul;8(8):1064-74
Impact factor: 7.345

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20. Clinical Events and Patient-Reported Chest Pain in All-Comers Treated With Resolute Integrity and Promus Element Stents: 2-Year Follow-Up of the DUTCH PEERS (DUrable Polymer-Based STent CHallenge of Promus ElemEnt Versus ReSolute Integrity) Randomized Trial (TWENTE II)

Sen H, Lam MK, Lowik MM, Danse PW, Jessurun GA, van Houwelingen KG, Anthonio RL, Tjon Joe Gin RM, Hautvast RW, Louwerenburg JH, de Man FH, Stoel MG, van der Heijden LC, Linssen GC, IJzerman MJ, Tandjung K, Doggen CJ, von Birgelen C

Objectives: This study assessed clinical events and patient-reported chest pain 2 years after treatment of all-comers with Resolute Integrity zotarolimus-eluting stents (Medtronic Vascular, Santa Rosa, California) and Promus Element everolimus-eluting stents (Boston Scientific, Natick, Massachusetts).
Background: For both drug-eluting stents (DES), no all-comer outcome data from >12 months of follow-up have been published. Although there is increasing interest in patient-reported chest pain following stenting, data with novel DES are scarce.
Methods: The DUTCH PEERS multicenter trial (TWENTE II) (DUrable Polymer-Based STent CHallenge of Promus ElemEnt Versus ReSolute Integrity) Randomized Trial [TWENTE II]) randomized 1,811 all-comer patients to treatment with 1 type of DES. Monitoring and event adjudication were performed by independent contract research organizations.
Results: The 2-year follow-up of 1,810 patients (99.9%) was available. The primary composite endpoint target vessel failure occurred in 8.6% and 7.8% of patients treated with zotarolimus- and everolimus-eluting stents, respectively (p = 0.55). Rates of components of target vessel failure were: cardiac death (2.4% vs. 1.9%, p = 0.42); target vessel-related myocardial infarction (2.4% vs. 1.8%, p = 0.33); clinically-indicated target vessel revascularization (4.6% vs. 4.9%, p = 0.83). At 1- and 2-year follow-up, >80% of patients were free from chest pain (no between-stent difference). In addition, >87% of patients were either free from chest pain or experienced pain only at maximal physical exertion, but not during normal daily activities. Patients with chest pain after 12 months at no more than moderate physical effort had a higher risk of target vessel revascularization during the following year (hazard ratio: 1.89 [95% confidence interval: 1.05 to 3.39], p = 0.03).
Conclusions: During the second year of follow-up, the incidence of adverse clinical endpoints remained similar and low for both DES. The vast majority of patients were free from chest pain.

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Impact factor: 7.345

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21. Complex patients treated with zotarolimus-eluting resolute and everolimus-eluting xience V stents in the randomized TWENTE trial: Comparison of 2-year clinical outcome
Sen H, Lam MK, Tandjung K, Lowik MM, Stoel MG, de Man FH, Louwerenburg JH, van Houwelingen GK, Linssen GC, Doggen CJ, Basalus MW, von Birgelen C

Objective: To assess the differences in clinical outcome between complex patients treated with Resolute zotarolimus-eluting stents (ZES) versus Xience V everolimus-eluting stents (EES).
Background: Nowadays, many complex patients with coronary disease are treated with percutaneous coronary interventions, using drug-eluting stents (DES).

Methods: We analyzed 2-year outcome data of 1,033 complex patients of the TWENTE trial, treated with second-generation Resolute ZES or Xience V EES. Complex patients had at least one of the following characteristics: renal insufficiency (creatinine >/= 140 micromol/l); ejection fraction < 30%; acute myocardial infarction (MI) within previous 72 hrs; >1 lesion/vessel; >2 vessels treated; lesion length > 27 mm; bifurcation; saphenous vein graft lesion; arterial bypass graft lesion; in-stent restenosis; unprotected left main lesion; lesion with thrombus; or lesion with total occlusion. Target vessel failure (TVF), the primary composite endpoint of the trial, was defined as cardiac death, target vessel-related MI, or target vessel revascularization.
Results: Among the 1,033 complex patients, 529 (51%) were treated with Resolute ZES and 504 (49%) with Xience V EES. Patient- and procedure-related characteristics were similar between DES groups. After 2-year follow-up, outcome was also similar between DES groups. TVF occurred in 12.1% of patients treated with Resolute ZES and 12.3% of patients treated with Xience V EES. In addition, DES groups did not differ significantly in cardiac death, MI, or target vessel revascularization-the individual components of TVF.
Conclusion: Complex patients treated with Resolute ZES and Xience V EES showed similar safety and efficacy during 2-year follow-up.

Gepubliceerd: Catheter Cardiovasc Interv 2015 Feb 28;85(1):74-81
Impact factor: 2.107

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22. Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects
Teuwen CP, Ramdjan TT, Gotte M, Brundel BJ, Evertz R, Vriend JW, Molhoek SG, Dorman HG, Van Opstal JM, Konings TC, van der Voort P, Delacretaz E, Houck C, Yaksh A, Jansz LJ, Witsenburg M, Roos-Hesselink JW, Triedman JK, Bogers AJ, de Groot NM

Background: The incidence of atrial fibrillation (AF) is rising in the aging patients with congenital heart defects (CHD). However, studies reporting on AF in patients with CHD are scarce. The aim of this multicenter study was to examine in a large cohort of patients with a variety of CHD: (1) the age of onset and initial treatment of AF, coexistence of atrial tachyarrhythmia and (2) progression of paroxysmal to (long-standing) persistent/permanent AF during long-term follow-up.
Methods and Results: Patients (n=199) with 15 different CHD and documented AF episodes were studied. AF developed at 49+/-17 years. Regular atrial tachycardia (AT) coexisting with AF occurred in 65 (33%) patients; 65% initially presented with regular AT. At the end of a follow-up period of 5 (0-24) years, the ECG showed AF in 81 patients (41%). In a subgroup of 114 patients, deterioration from paroxysm of AF to (long-standing) persistent/permanent AF was observed in 29 patients (26%) after only 3 (0-18) years of the first AF episode. Cerebrovascular accidents/transient ischemic attacks occurred in 26 patients (13%), although a substantial number (n=16) occurred before the first documented AF episode.
Conclusions: Age at development of AF in patients with CHD is relatively young compared with the patients without CHD. Coexistence of episodes of AF and regular AT occurred in a considerable number of patients; most of them initially presented

with regular AT. The fast and frequent progression from paroxysmal to (long-standing) persistent or permanent AF episodes justifies close follow-up and early, aggressive therapy of both AT and AF.

Gepubliceerd: Circ Arrhythm Electrophysiol 2015 Oct;8(5):1065-72
Impact factor: 4.678

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23. Fractional Flow Reserve and Coronary Bifurcation Anatomy: A Novel Quantitative Model to Assess and Report the Stenosis Severity of Bifurcation Lesions
Tu S, Echavarria-Pinto M, von Birgelen C, Holm NR, Pyxaras SA, Kumsars I, Lam MK, Valkenburg I, Toth GG, Li Y, Escaned J, Wijns W, Reiber JH

Objectives: The aim of this study was to develop a new model for assessment of stenosis severity in a bifurcation lesion including its core. The diagnostic performance of this model, powered by 3-dimensional quantitative coronary angiography to predict the functional significance of obstructive bifurcation stenoses, was evaluated using fractional flow reserve (FFR) as the reference standard.
Background: Development of advanced quantitative models might help to establish a relationship between bifurcation anatomy and FFR.
Methods: Patients who had undergone coronary angiography and interventions in 5 European cardiology centers were randomly selected and analyzed. Different bifurcation fractal laws, including Murray, Finet, and HK laws, were implemented in the bifurcation model, resulting in different degrees of stenosis severity.
Results: A total of 78 bifurcation lesions in 73 patients were analyzed. In 51 (65%) bifurcations, FFR was measured in the main vessel. A total of 34 (43.6%) interrogated vessels had an FFR </=0.80. Correlation between FFR and diameter stenosis was poor by conventional straight analysis (rho = -0.23, $p < 0.001$) but significantly improved by bifurcation analyses: the highest by the HK law (rho = -0.50, $p < 0.001$), followed by the Finet law (rho = -0.49, $p < 0.001$), and the Murray law (rho = -0.41, $p < 0.001$). The area under the receiver-operating characteristics curve for predicting FFR </=0.80 was significantly higher by bifurcation analysis compared with straight analysis: 0.72 (95% confidence interval: 0.61 to 0.82) versus 0.60 (95% confidence interval: 0.49 to 0.71; $p = 0.001$). Applying a threshold of >/=50% diameter stenosis, as assessed by the bifurcation model, to predict FFR </=0.80 resulted in 23 true positives, 27 true negatives, 17 false positives, and 11 false negatives.
Conclusions: The new bifurcation model provides a comprehensive assessment of bifurcation anatomy. Compared with straight analysis, identification of lesions with preserved FFR values in obstructive bifurcation stenoses was improved. Nevertheless, accuracy was limited by using solely anatomical parameters.

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Impact factor: 7.345

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24. Non-intubated recovery from refractory cardiogenic shock on percutaneous VA-extracorporeal membrane oxygenation
van Houte J, Donker DW, Wagenaar LJ, Slootweg AP, Kirkels JH, van Dijk D

We report on the use of percutaneous femoral veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in a fully awake, non-intubated and spontaneously breathing patient suffering from acute, severe and refractory cardiogenic shock due to a (sub)acute anterior myocardial infarction. Intensified heart failure therapy was closely monitored with a pulmonary artery catheter and allowed gradual weaning off the ECMO support without additional invasive measures, notably without mechanical ventilation. Neurological assessment was possible at all times and complete physical mobilisation was straightforward directly after weaning from ECMO. This limited invasive approach may encourage a more widespread use of percutaneous VA-ECMO.

Gepubliceerd: Neth Heart J 2015 Jul;23(7-8):386-8
Impact factor: 1.837

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25. Three-year clinical outcome after treatment of chronic total occlusions with Second-generation drug-eluting stents in the TWENTE trial
van Houwelingen KG, Sen H, Lam MK, Tandjung K, Lowik MM, de Man FH, Louwerenburg JH, Stoel MG, Hartmann M, Linssen GC, Doggen CJ, von Birgelen C

Objective: To compare long-term outcome of patients treated for chronic total occlusion (CTO) lesions versus patients treated for non-CTO lesions only.
Background: Percutaneous coronary interventions (PCI) for CTO lesions generally have a higher adverse event risk than PCI for non-CTO lesions. However, long-term outcome data from prospective studies with second-generation drug-eluting stent (DES) use in CTO lesions is scarce.
Methods: We analyzed in this sub-study of the TWENTE trial the data of 674 patients, who had stable angina and were electively treated with second-generation DES (Resolute zotarolimus-eluting or Xience V everolimus-eluting stents). Main outcome parameter was target lesion failure (TLF), a composite of cardiac death, target vessel-related myocardial infarction, or target lesion revascularization (TLR).
Results: Patients with CTO lesions (n=59, 8.8%) were more often treated for lesions in small vessels (94.9% vs. 63.1%, p<0.001), long lesions (52.5% vs. 17.7%, p<0.001) and multiple vessels (42.4% vs. 22.4%, p<0.001), and were less often males (62.7% vs. 74.6%, p<0.05) than patients with non-CTO lesions (n=615, 91.2%). J-CTO scores >/=2 were present in 56% of CTO lesions. Despite significant differences in characteristics of patients, lesions, and interventional procedures, the TLF rate at 3-year follow-up was similar for both groups (13.6% vs. 12.9%, p=0.89). In addition, a patient-oriented composite endpoint (any death, MI or revascularization) did not differ between groups (18.6% vs. 18.8%, p=0.97).
Conclusion: Patients treated with second-generation DES for CTO lesions showed at 3-year follow-up an incidence of adverse clinical events that was low and similar to patients with non-CTO lesions only. (c) 2014 Wiley Periodicals, Inc.

Gepubliceerd: Catheter Cardiovasc Interv 2015;85(3):E76-E82
Impact factor: 2.107

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26. Lifetime Risk of Pulmonary Hypertension for All Patients After Shunt Closure
van Riel AC, Blok IM, Zwinderman AH, Wajon EM, Sadee AS, Bakker-de Boo M, van Dijk AP, Hoendermis ES, Riezebos RK, Mulder BJ, Bouma BJ

Gepubliceerd: J Am Coll Cardiol 2015 Sep 1;66(9):1084-6
Impact factor: 16.503

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27. Reply: Post-Percutaneous Coronary Intervention Angina: A New Performance Measure?
von Birgelen C, van der Heijden LC, Sen H, Lowik MM

Gepubliceerd: JACC Cardiovasc Interv 2015 Oct;8(12):1640-1
Impact factor: 7.345

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28. How should I treat multiple coronary aneurysms with severe stenoses?
Warisawa T, Naganuma T, Nakamura S, Hartmann M, Stoel MG, Louwerenburg JH, Basalus MW, von Birgelen C, Koo BK

Gepubliceerd: EuroIntervention 2015 Nov 22;11(8):843-6
Impact factor: 3.769

Totale impact factor: 141.399
Gemiddelde impact factor: 5.050

Aantal artikelen 1e, 2e of laatste auteur: 15
Totale impact factor: 65.448
Gemiddelde impact factor: 4.363

Gynaecologie

1. Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation
Bensdorp AJ, Tjon-Kon-Fat RI, Bossuyt PM, Koks CA, Oosterhuis GJ, Hoek A, Hompes PG, Broekmans FJ, Verhoeve HR, de Bruin JP, van Golde R, Repping S, Cohlen BJ, Lambers MD, van Bommel PF, Slappendel E, Perquin D, Smeenk JM, Pelinck MJ, Gianotten J, Hoozemans DA, Maas JW, Eijkemans MJ, van der Valk PD, Mol BW, van Wely M

Objectives: To compare the effectiveness of in vitro fertilisation with single embryo transfer or in vitro fertilisation in a modified natural cycle with that of intrauterine insemination with controlled ovarian hyperstimulation in terms of a healthy child.
Design: Multicentre, open label, three arm, parallel group, randomised controlled non-inferiority trial.
Setting: 17 centres in the Netherlands.
Participants: Couples seeking fertility treatment after at least 12 months of unprotected intercourse, with the female partner aged between 18 and 38 years, an unfavourable prognosis for natural conception, and a diagnosis of unexplained or mild male subfertility.
Interventions: Three cycles of in vitro fertilisation with single embryo transfer (plus subsequent cryocycles), six cycles of in vitro fertilisation in a modified natural cycle, or six cycles of intrauterine insemination with ovarian hyperstimulation within 12 months after randomisation.
Main outcome measures: The primary outcome was birth of a healthy child resulting from a singleton pregnancy conceived within 12 months after randomisation. Secondary outcomes were live birth, clinical pregnancy, ongoing pregnancy, multiple pregnancy, time to pregnancy, complications of pregnancy, and neonatal morbidity and mortality
Results: 602 couples were randomly assigned between January 2009 and February 2012; 201 were allocated to in vitro fertilisation with single embryo transfer, 194 to in vitro fertilisation in a modified natural cycle, and 207 to intrauterine insemination with controlled ovarian hyperstimulation. Birth of a healthy child occurred in 104 (52%) couples in the in vitro fertilisation with single embryo transfer group, 83 (43%) in the in vitro fertilisation in a modified natural cycle group, and 97 (47%) in the intrauterine insemination with controlled ovarian hyperstimulation group. This corresponds to a risk, relative to intrauterine insemination with ovarian hyperstimulation, of 1.10 (95% confidence interval 0.91 to 1.34) for in vitro fertilisation with single embryo transfer and 0.91 (0.73 to 1.14) for in vitro fertilisation in a modified natural cycle. These 95% confidence intervals do not extend below the predefined threshold of 0.69 for inferiority. Multiple pregnancy rates per ongoing pregnancy were 6% (7/121) after in vitro fertilisation with single embryo transfer, 5% (5/102) after in vitro fertilisation in a modified natural cycle, and 7% (8/119) after intrauterine insemination with ovarian hyperstimulation (one sided P=0.52 for in vitro fertilisation with single embryo transfer compared with intrauterine insemination with ovarian hyperstimulation; one

sided P=0.33 for in vitro fertilisation in a modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation).
Conclusions: In vitro fertilisation with single embryo transfer and in vitro fertilisation in a modified natural cycle were non-inferior to intrauterine insemination with controlled ovarian hyperstimulation in terms of the birth of a healthy child and showed comparable, low multiple pregnancy rates.Trial registration Current Controlled Trials ISRCTN52843371; Nederlands Trial Register NTR939.

Gepubliceerd: BMJ 2015;350:g7771
Impact factor: 17.400

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2. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial
Broekhuijsen K, van Baaren GJ, van Pampus MG, Ganzevoort W, Sikkema JM, Woiski MD, Oudijk MA, Bloemenkamp KW, Scheepers HC, Bremer HA, Rijnders RJ, van Loon AJ, Perquin DA, Sporken JM, Papatsonis DN, van Huizen ME, Vredevoogd CB, Brons JT, Kaplan M, van Kaam AH, Groen H, Porath MM, van den Berg PP, Mol BW, Franssen MT, Langenveld J

Background: There is little evidence to guide the management of women with hypertensive disorders in late preterm pregnancy. We investigated the effect of immediate delivery versus expectant monitoring on maternal and neonatal outcomes in such women.
Methods: We did an open-label, randomised controlled trial, in seven academic hospitals and 44 non-academic hospitals in the Netherlands. Women with non-severe hypertensive disorders of pregnancy between 34 and 37 weeks of gestation were randomly allocated to either induction of labour or caesarean section within 24 h (immediate delivery) or a strategy aimed at prolonging pregnancy until 37 weeks of gestation (expectant monitoring). The primary outcomes were a composite of adverse maternal outcomes (thromboembolic disease, pulmonary oedema, eclampsia, HELLP syndrome, placental abruption, or maternal death), and neonatal respiratory distress syndrome, both analysed by intention-to-treat. This study is registered with the Netherlands Trial Register (NTR1792).
Findings: Between March 1, 2009, and Feb 21, 2013, 897 women were invited to participate, of whom 703 were enrolled and randomly assigned to immediate delivery (n=352) or expectant monitoring (n=351). The composite adverse maternal outcome occurred in four (1.1%) of 352 women allocated to immediate delivery versus 11 (3.1%) of 351 women allocated to expectant monitoring (relative risk [RR] 0.36, 95% CI 0.12-1.11; p=0.069). Respiratory distress syndrome was diagnosed in 20 (5.7%) of 352 neonates in the immediate delivery group versus six (1.7%) of 351 neonates in the expectant monitoring group (RR 3.3, 95% CI 1.4-8.2; p=0.005). No maternal or perinatal deaths occurred.
Interpretation: For women with non-severe hypertensive disorders at 34-37 weeks of gestation, immediate delivery might reduce the already small risk of adverse maternal outcomes. However, it significantly increases the risk of neonatal respiratory distress syndrome, therefore, routine immediate delivery does not seem

justified and a strategy of expectant monitoring until the clinical situation deteriorates can be considered.
Funding: ZonMw.

Gepubliceerd: Lancet 2015 Mar 24;385(9986):2492-501
Impact factor: 45.217

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3. Patient satisfaction and amenorrhea rate after endometrial ablation by ThermaChoice III or NovaSure: a retrospective cohort study

Muller I, van der Palen J, Massop-Helmink D, Vos-de Bruin R, Sikkema JM

Heavy menstrual bleeding poses an important health problem, which can be managed, besides other treatments, with endometrial ablation. Nowadays, the bipolar radio frequency device (NovaSure) is the most commonly used device for endometrial ablation, followed by the thermal balloon device (ThermaChoice III). Thus far, studies looking at treatment outcomes have mainly been done comparing NovaSure with the older ThermaChoice (I–II) devices. The aim of this study is to compare the effectiveness of the improved ThermaChoice III with NovaSure. Patients treated with ThermaChoice III at the Ziekenhuisgroep Twente hospital and NovaSure at the Medisch Spectrum Twente hospital were included in the study. The primary outcome measure was patient satisfaction after treatment, measured by the condition-specific menorrhagia multi-attribute scale (MMAS). The secondary outcome measure was effectiveness of the treatment, measured by the amenorrhea rate and the hysterectomy rate. Five hundred fourteen patients were included in this study; of these, 216 patients were treated with ThermaChoice III and 289 patients with NovaSure. The score on the condition-specific MMAS was high for both groups, without a significant difference between the groups (88.8 vs 86.5, p?=?0.183). The amenorrhea rate was significantly higher in the NovaSure group (45 vs 27 %, p?=?0.001). The hysterectomy rate was slightly higher in the ThermaChoice III group, without a significant difference between the groups (19 compared to 13 %, p?=?0.066). Patient satisfaction is comparable in patients treated with ThermaChoice III or NovaSure. However, NovaSure endometrial ablation leads to a significantly higher amenorrhea rate.

Gepubliceerd: Gynecol Surg 2015;12(81):87
Impact factor: 0

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4. Is IVF-served two different ways-more cost-effective than IUI with controlled ovarian hyperstimulation?
Tjon-Kon-Fat RI, Bensdorp AJ, Bossuyt PM, Koks C, Oosterhuis GJ, Hoek A, Hompes P, Broekmans FJ, Verhoeve HR, de Bruin JP, van Golde R, Repping S, Cohlen BJ, Lambers MD, van Bommel PF, Slappendel E, Perquin D, Smeenk J, Pelinck MJ, Gianotten J, Hoozemans DA, Maas JW, Groen H, Eijkemans MJ, van der Valk PD, Mol BW, van Wely M

Study question: What is the cost-effectiveness of in vitro fertilization (IVF) with conventional ovarian stimulation, single embryo transfer (SET) and subsequent cryocycles or IVF in a modified natural cycle (MNC) compared with intrauterine insemination with controlled ovarian hyperstimulation (IUI-COH) as a first-line treatment in couples with unexplained subfertility and an unfavourable prognosis on natural conception?.
Summary answer: Both IVF strategies are significantly more expensive when compared with IUI-COH, without being significantly more effective. In the comparison between IVF-MNC and IUI-COH, the latter is the dominant strategy. Whether IVF-SET is cost-effective depends on society's willingness to pay for an additional healthy child.
What is known already: IUI-COH and IVF, either after conventional ovarian stimulation or in a MNC, are used as first-line treatments for couples with unexplained or mild male subfertility. As IUI-COH is less invasive, this treatment is usually offered before proceeding to IVF. Yet, as conventional IVF with SET may lead to higher pregnancy rates in fewer cycles for a lower multiple pregnancy rate, some have argued to start with IVF instead of IUI-COH. In addition, IVF in the MNC is considered to be a more patient friendly and less costly form of IVF.
Study design, size, duration: We performed a cost-effectiveness analysis alongside a randomized noninferiority trial. Between January 2009 and February 2012, 602 couples with unexplained infertility and a poor prognosis on natural conception were allocated to three cycles of IVF-SET including frozen embryo transfers, six cycles of IVF-MNC or six cycles of IUI-COH. These couples were followed until 12 months after randomization.
Participants/materials, setting, methods: We collected data on resource use related to treatment, medication and pregnancy from the case report forms. We calculated unit costs from various sources. For each of the three strategies, we calculated the mean costs and effectiveness. Incremental cost-effectiveness ratios (ICER) were calculated for IVF-SET compared with IUI-COH and for IVF-MNC compared with IUI-COH. Nonparametric bootstrap resampling was used to investigate the effect of uncertainty in our estimates.
Main results and the role of chance: There were 104 healthy children (52%) born in the IVF-SET group, 83 (43%) the IVF-MNC group and 97 (47%) in the IUI-COH group. The mean costs per couple were euro7187 for IVF-SET, euro8206 for IVF-MNC and euro5070 for IUI-COH. Compared with IUI-COH, the costs for IVF-SET and IVF-MNC were significantly higher (mean differences euro2117; 95% CI: euro1544-euro2657 and euro3136, 95% CI: euro2519-euro3754, respectively).The ICER for IVF-SET compared with IUI-COH was euro43 375 for the birth of an additional healthy child. In the comparison of IVF-MNC to IUI-COH, the latter was the dominant strategy, i.e. more effective at lower costs.
Limitations, reasons for caution: We only report on direct health care costs. The present analysis is limited to 12 months.
Wider implications of the findings: Since we found no evidence in support of offering IVF as a first-line strategy in couples with unexplained and mild subfertility, IUI-COH should remain the treatment of first choice.
Study funding/competing interests: The study was supported by a grant from ZonMw, the Netherlands Organization for Health Research and Development,

(120620027) and a grant from Zorgverzekeraars Nederland, the Netherlands' association of health care insurers (09-003).
Trial registration number: Current Controlled Trials ISRCTN52843371; Nederlands Trial Register NTR939.

Gepubliceerd: Hum Reprod 2015 Oct;30(10):2331-9
Impact factor: 4.569

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5. The HysNiche trial: hysteroscopic resection of uterine caesarean scar defect (niche) in patients with abnormal bleeding, a randomised controlled trial

Vervoort AJ, Van der Voet LF, Witmer M, Thurkow AL, Radder CM, van Kesteren PJ, Quartero HW, Kuchenbecker WK, Bongers MY, Geomini PM, de Vleeschouwer LH, van Hooff MH, van Vliet HA, Veersema S, Renes WB, van Meurs HS, Bosmans J, Oude Rengerink K, Brolmann HA, Mol BW, Huirne JA

Background: A caesarean section (CS) can cause a defect or disruption of the myometrium at the site of the uterine scar, called a niche. In recent years, an association between a niche and postmenstrual spotting after a CS has been demonstrated. Hysteroscopic resection of these niches is thought to reduce spotting and menstrual pain. However, there are no randomised trials assessing the effectiveness of a hysteroscopic niche resection.
Mehtods/Design: We planned a multicentre randomised trial comparing hysteroscopic niche resection to no intervention. We study women with postmenstrual spotting after a CS and a niche with a residual myometrium of at least 3 mm during sonohysterography. After informed consent is obtained, eligible women will be randomly allocated to hysteroscopic resection of the niche or expectant management for 6 months. The primary outcome is the number of days with postmenstrual spotting during one menstrual cycle 6 months after randomisation. Secondary outcomes are menstrual characteristics, menstruation related pain and experienced discomfort due to spotting or menstrual pain, quality of life, patient satisfaction, sexual function, urological symptoms, medical consultations, medication use, complications, lost productivity and medical costs. Measurements will be performed at baseline and at 3 and 6 months after randomisation. A cost-effectiveness analysis will be performed from a societal perspective at 6 months after randomisation.
Discussion: This trial will provide insight in the (cost)effectiveness of hysteroscopic resection of a niche versus expectant management in women who have postmenstrual spotting and a niche with sufficient residual myometrium to perform a hysteroscopic niche resection.
Trial registration: Dutch Trial Register NTR3269 . Registered 1 February 2012. ZonMw Grant number 80-82305-97-12030.

Gepubliceerd: BMC Womens Health 2015;15(1):103
Impact factor: 1.495

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6. Gonadotrophins for ovulation induction in women with polycystic ovarian syndrome

Weiss NS, Nahuis M, Bayram N, Mol BW, Van der Veen F, van Wely M

Background: Ovulation induction with follicle stimulating hormone (FSH) is the second-line treatment in women with polycystic ovary syndrome (PCOS) who do not ovulate or conceive on clomiphene citrate (CC).
Objectives: To compare the effectiveness and safety of gonadotrophins as a second-line treatment for ovulation induction in women with CC-resistant PCOS.
Search methods: We searched the Menstrual Disorders & Subfertility Group's Specialist Register of controlled trials, the Cochrane Central Register of Controlled Trials, MEDLINE (1966 to October 2014), EMBASE (1980 to October 2014), CINAHL (1982 to October 2014), National Research Register and web-based trials databases such as Current Controlled Trials. There was no language restriction.
Selection criteria: All randomised controlled trials reporting data on comparing clinical outcomes in women with PCOS who did not ovulate or conceive on CC, and undergoing ovulation induction with urinary FSH (uFSH: FSH-P or FSH-HP), HMG/HP-HMG or recombinant FSH. We included trials reporting on ovulation induction followed by intercourse or intrauterine insemination. We excluded studies that used co-treatment with CC, metformin, LH or letrozole.
Data collection and analysis: Three review authors (NW, MN and MvW) independently selected studies for inclusion, assessed study quality and extracted study data. Primary outcomes were live birth rate per woman (effectiveness outcome) and incidence of ovarian hyperstimulation syndrome (OHSS) per woman (safety outcome). Secondary outcomes were clinical pregnancy, miscarriage, multiple pregnancy, total gonadotrophin dose and total duration of stimulation per woman. We combined data using a fixed-effect model to calculate the odds ratio (OR). We summarised the overall quality of evidence for the main outcomes using GRADE criteria. MAIN
Results: The review includes 14 trials with 1726 women. Ten trials compared rFSH versus urinary-derived gonadotrophins (three rFSH versus HMG and seven rFSH versus FSH-HP), four trials compared FSH-P with HMG. We found no trials that compared FSH-HP with FSH-P.We found no evidence of a difference in live birth for rFSH versus urinary-derived gonadotrophins (OR 1.26, 95% CI 0.80 to 1.99, 5 trials, 505 women, I(2) = 0%, low-quality evidence) or clinical pregnancy rate (OR 1.08, 95% CI 0.83 to 1.39, 8 trials, 1330 women, I(2) = 0, low-quality evidence). This suggests that for the observed average live birth per woman with urinary-derived FSH of 16%, the chance of live birth following rFSH is between 13% and 26%.For the comparison HMG or HP-HMG versus FSH-P there was also no difference in the evidence on live birth rate (OR 1.36, 95% CI 0.58 to 3.18, 3 trials, 138 women, I(2) = 0%, low-quality evidence). This suggests that for a woman with a live birth rate of 18% with HMG or HP-HMG, the chance of live birth following uFSH is between 9% and 37%.Trial authors used various definitions for OHSS. Pooling the data, we found no evidence of a difference for rFSH versus urinary-derived gonadotrophins (OR 1.52, 95% CI 0.81 to 2.84, 10 trials, 1565 women, I2 = 0%, very low-quality evidence) and for HMG or HP-HMG versus FSH-P (OR 9.95, 95% CI 0.47 to 210.19, 2 trials, 53 women, I(2) = 0%, very low-quality evidence).

Author's conclusions: In women with PCOS and CC resistance or CC failure, we found no evidence of a difference in live birth and OHSS rates between urinary-derived gonadotrophins and rFSH or HMG/HP-HMG. Evidence for all outcomes was of low or very low quality. We suggest weighing costs and convenience in the decision to use one or the other.

Gepubliceerd: Cochrane Database Syst Rev 2015 Sep 9;9:CD010290
Impact factor: 6.035

Totale impact factor: 74.716
Gemiddelde impact factor: 12.453

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

Heelkunde

1. Meta-analysis of superficial versus deep injection of radioactive tracer and blue dye for lymphatic mapping and detection of sentinel lymph nodes in breast cancer
Ahmed M, Purushotham AD, Horgan K, Klaase JM, Douek M

Background: Sentinel lymph node biopsy (SLNB) is the standard of care for axillary staging in early breast cancer. Currently, no consensus exists on the optimal site of injection of the radioactive tracer or blue dye.
Methods: A systematic review and meta-analysis of studies comparing superficial and deep injections of radioactive tracer or blue dye for lymphatic mapping and SLNB was performed. The axillary and extra-axillary sentinel lymph node (SLN) identification rates obtained by lymphoscintigraphy and intraoperative SLNB were evaluated. Pooled odds ratios (ORs) and 95 per cent c.i. were estimated using fixed-effect analyses, or random-effects analyses if there was statistically significant heterogeneity ($P < 0.050$).
Results: Thirteen studies were included in the meta-analysis. There was no significant difference between superficial and deep injections of radioactive tracer for axillary SLN identification on lymphoscintigraphy (OR 1.59, 95 per cent c.i. 0.79 to 3.17), during surgery (OR 1.27, 0.60 to 2.68) and for SLN identification using blue dye (OR 1.40, 0.83 to 2.35). The rate of extra-axillary SLN identification was significantly greater when deep rather than superficial injection was used (OR 3.00, 1.92 to 4.67). The discordance rate between superficial and deep injections ranged from 4 to 73 per cent for axillary and from 0 to 61 per cent for internal mammary node mapping.
Conclusion: Both superficial and deep injections of radioactive tracer and blue dye are effective for axillary SLN identification. Clinical consequences of discordance rates between the two injection techniques are unclear. Deep injections are associated with significantly greater extra-axillary SLN identification; however, this may not have a significant impact on clinical management.

Gepubliceerd: Br J Surg 2015;102(3):169-81
Impact factor: 5.542

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2. Surgical treatment of nonpalpable primary invasive and in situ breast cancer
Ahmed M, Rubio IT, Klaase JM, Douek M

Breast cancer is the most-common cancer among women worldwide, and over one-third of all cases diagnosed annually are nonpalpable at diagnosis. The increasingly widespread implementation of breast-screening programmes, combined with the use of advanced imaging modalities, such as magnetic resonance imaging (MRI), will further increase the numbers of patients diagnosed with this disease. The current standard management for nonpalpable breast cancer is localized surgical excision combined with axillary staging, using sentinel-lymph-node biopsy in the clinically and

radiologically normal axilla. Wire-guided localization (WGL) during mammography is a method that was developed over 40 years ago to enable lesion localization preoperatively; this technique became the standard of care in the absence of a better alternative. Over the past 20 years, however, other technologies have been developed as alternatives to WGL in order to overcome the technical and outcome-related limitations of this technique. This Review discusses the techniques available for the surgical management of nonpalpable breast cancer; we describe their advantages and disadvantages, and highlight future directions for the development of new technologies.

Gepubliceerd: Nat Rev Clin Oncol 2015 Sep 29;12(11):645-63
Impact factor: 14.180

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3. Neo-adjuvant chemotherapy followed by surgery versus surgery alone in high-risk patients with resectable colorectal liver metastases: the CHARISMA randomized multicenter clinical trial

Ayez N, van der Stok EP, de Wilt H, Radema SA, van Hillegersberg R, Roumen RM, Vreugdenhil G, Tanis PJ, Punt CJ, De Jong CA, Jansen RL, Verheul HM, de Jong KP, Hospers GA, Klaase JM, Legdeur MC, van Meerten E, Eskens FA, van der Meer N, van der Holt B, Verhoef C, Grunhagen DJ

Background: Efforts to improve the outcome of liver surgery by combining curative resection with chemotherapy have failed to demonstrate definite overall survival benefit. This may partly be due to the fact that these studies often involve strict inclusion criteria. Consequently, patients with a high risk profile as characterized by Fong's Clinical Risk Score (CRS) are often underrepresented in these studies. Conceptually, this group of patients might benefit the most from chemotherapy. The present study evaluates the impact of neo-adjuvant chemotherapy in high-risk patients with primary resectable colorectal liver metastases, without extrahepatic disease. Our hypothesis is that adding neo-adjuvant chemotherapy to surgery will provide an improvement in overall survival (OS) in patients with a high-risk profile.
Mehtods/Design: CHARISMA is a multicenter, randomized, phase III clinical trial. Patients will be randomized to either surgery alone (standard treatment, arm A) or to 6 cycles of neo-adjuvant oxaliplatin-based chemotherapy, followed by surgery (arm B). Patients must be >/= 18 years of age with liver metastases of histologically confirmed primary colorectal carcinoma. Patients with extrahepatic metastases are excluded. Liver metastases must be deemed primarily resectable. Only patients with a CRS of 3-5 are eligible. The primary study endpoint is OS. Secondary endpoints are progression free survival (PFS), quality of life, morbidity of resection, treatment response on neo-adjuvant chemotherapy, and whether CEA levels can predict treatment response.
Discussion: CHARISMA is a multicenter, randomized, phase III clinical trial that will provide an answer to the question if adding neo-adjuvant chemotherapy to surgery will improve OS in a well-defined high-risk patient group with colorectal liver metastases.

Trial registration: The CHARISMA is registered at European Union Clinical Trials Register (EudraCT), number: 2013-004952-39 and in the "Netherlands national Trial Register (NTR), number: 4893.

Gepubliceerd: BMC Cancer 2015;15:180
Impact factor: 3.362

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4. Rapid enzyme analysis as a diagnostic tool for wound infection: Comparison between clinical judgment, microbiological analysis and enzyme analysis
Blokhuis-Arkes MH, Haalboom M, van der Palen J, Heinzle A, Sigl E, Guebitz G, Beuk R

In clinical practice, diagnosis of wound infection is based on the classical clinical signs of infection. When infection is suspected, wounds are often swabbed for microbiological culturing. These methods are not accurate (clinical judgment in chronic wounds) or provide results after several days (wound swab). Therefore, there is an urgent need for an easy-to-use diagnostic tool for fast detection of wound infection, especially in chronic wounds. This study determined the diagnostic properties of the enzymes myeloperoxidase (MPO), human neutrophil elastase (HNE), lysozyme and cathepsin-G in detecting wound infection when compared to wound swabs. Both chronic and acute wounds of 81 patients were assessed through clinical judgment, enzyme analysis and wound swab. Three promising enzyme models for detecting wound infection were identified. A positive test was defined as: at least one enzyme positive after 30 minutes (model 1), lysozyme and HNE positive after 30 minutes (model 2), MPO positive after 5 minutes, and HNE or lysozyme positive after 30 minutes (model 3). All models were significant (p</=0.001). There was no correlation between clinical judgment and wound swab, indicating the need for novel diagnostic systems. Enzyme analysis is fast, easy to use and superior to clinical judgment when compared to wound swabs.

Gepubliceerd: Wound Repair Regen 2015 Mar 26;23(3):345-52
Impact factor: 2.745

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5. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial
da Costa DW, Bouwense SA, Schepers NJ, Besselink MG, van Santvoort HC, van Brunschot S, Bakker OJ, Bollen TL, De jong CH, van Goor H, Boermeester MA, Bruno MJ, van Eijck CH, Timmer R, Weusten BL, Consten EC, Brink MA, Spanier BW, Bilgen EJ, Nieuwenhuijs VB, Hofker HS, Rosman C, Voorburg AM, Bosscha K, van Duijvendijk P, Gerritsen JJ, Heisterkamp J, de Hingh IH, Witteman BJ, Kruyt PM, Scheepers JJ, Molenaar IQ, Schaapherder AF, Manusama ER, van der Waaij LA, van Unen J, Dijkgraaf MG, van Ramshorst B, Gooszen HG, Boerma D

Background: In patients with mild gallstone pancreatitis, cholecystectomy during the same hospital admission might reduce the risk of recurrent gallstone-related complications, compared with the more commonly used strategy of interval cholecystectomy. However, evidence to support same-admission cholecystectomy is poor, and concerns exist about an increased risk of cholecystectomy-related complications with this approach. In this study, we aimed to compare same-admission and interval cholecystectomy, with the hypothesis that same-admission cholecystectomy would reduce the risk of recurrent gallstone-related complications without increasing the difficulty of surgery.
Methods: For this multicentre, parallel-group, assessor-masked, randomised controlled superiority trial, inpatients recovering from mild gallstone pancreatitis at 23 hospitals in the Netherlands (with hospital discharge foreseen within 48 h) were assessed for eligibility. Adult patients (aged >/=18 years) were eligible for randomisation if they had a serum C-reactive protein concentration less than 100 mg/L, no need for opioid analgesics, and could tolerate a normal oral diet. Patients with American Society of Anesthesiologists (ASA) class III physical status who were older than 75 years of age, all ASA class IV patients, those with chronic pancreatitis, and those with ongoing alcohol misuse were excluded. A central study coordinator randomly assigned eligible patients (1:1) by computer-based randomisation, with varying block sizes of two and four patients, to cholecystectomy within 3 days of randomisation (same-admission cholecystectomy) or to discharge and cholecystectomy 25-30 days after randomisation (interval cholecystectomy). Randomisation was stratified by centre and by whether or not endoscopic sphincterotomy had been done. Neither investigators nor participants were masked to group assignment. The primary endpoint was a composite of readmission for recurrent gallstone-related complications (pancreatitis, cholangitis, cholecystitis, choledocholithiasis needing endoscopic intervention, or gallstone colic) or mortality within 6 months after randomisation, analysed by intention to treat. The trial was designed to reduce the incidence of the primary endpoint from 8% in the interval group to 1% in the same-admission group. Safety endpoints included bile duct leakage and other complications necessitating re-intervention. This trial is registered with Current Controlled Trials, number ISRCTN72764151, and is complete.
Findings: Between Dec 22, 2010, and Aug 19, 2013, 266 inpatients from 23 hospitals in the Netherlands were randomly assigned to interval cholecystectomy (n=137) or same-admission cholecystectomy (n=129). One patient from each group was excluded from the final analyses, because of an incorrect diagnosis of pancreatitis in one patient (in the interval group) and discontinued follow-up in the other (in the same-admission group). The primary endpoint occurred in 23 (17%) of 136 patients in the interval group and in six (5%) of 128 patients in the same-admission group (risk ratio 0.28, 95% CI 0.12-0.66; p=0.002). Safety endpoints occurred in four patients: one case of bile duct leakage and one case of postoperative bleeding in each group. All of these were serious adverse events and were judged to be treatment related, but none led to death.
Interpretation: Compared with interval cholecystectomy, same-admission cholecystectomy reduced the rate of recurrent gallstone-related complications in patients with mild gallstone pancreatitis, with a very low risk of cholecystectomy-related complications.
Funding: Dutch Digestive Disease Foundation.

Gepubliceerd: Lancet 2015 Sep 26;386(10000):1261-8
Impact factor: 45.217

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6. A Nationwide Comparison of Laparoscopic and Open Distal Pancreatectomy for Benign and Malignant Disease
de Rooij T, Jilesen AP, Boerma D, Bonsing BA, Bosscha K, van Dam RM, van Dieren S, Dijkgraaf MG, van Eijck CH, Gerhards MF, van Goor H, van der Harst E, de Hingh IH, Kazemier G, Klaase JM, Molenaar IQ, Nieveen van Dijkum EJ, Patijn GA, van Santvoort HC, Scheepers JJ, van der Schelling GP, Sieders E, Vogel JA, Busch OR, Besselink MG

Background: Cohort studies from expert centers suggest that laparoscopic distal pancreatectomy (LDP) is superior to open distal pancreatectomy (ODP) regarding postoperative morbidity and length of hospital stay. But the generalizability of these findings is unknown because nationwide data on LDP are lacking.
Study Design: Adults who had undergone distal pancreatectomy in 17 centers between 2005 and 2013 were analyzed retrospectively. First, all LDPs were compared with all ODPs. Second, groups were matched using a propensity score. Third, the attitudes of pancreatic surgeons toward LDP were surveyed. The primary outcome was major complications (Clavien-Dindo grade >/=III).
Results: Among 633 included patients, 64 patients (10%) had undergone LDP and 569 patients (90%) had undergone ODP. Baseline characteristics were comparable, except for previous abdominal surgery and mean tumor size. In the full cohort, LDP was associated with fewer major complications (16% vs 29%; p = 0.02) and a shorter median [interquartile range, IQR] hospital stay (8 days [7-12 days] vs 10 days [8-14 days]; p = 0.03). Of all LDPs, 33% were converted to ODP. Matching succeeded for 63 LDP patients. After matching, the differences in major complications (9 patients [14%] vs 19 patients [30%]; p = 0.06) and median [IQR] length of hospital stay (8 days [7-12 days] vs 10 days [8-14 days]; p = 0.48) were not statistically significant. The survey demonstrated that 85% of surgeons welcomed LDP training.
Conclusions: Despite nationwide underuse and an impact of selection bias, outcomes of LDP seemed to be at least noninferior to ODP. Specific training is welcomed and could improve both the use and outcomes of LDP.

Gepubliceerd: J Am Coll Surg 2015;220(3):263-70
Impact factor: 5.122

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7. Trauma team activation varies across Dutch emergency departments: a national survey
Egberink RE, Otten HJ, IJzerman MJ, van Vugt AB, Doggen CJ

Background: Tiered trauma team response may contribute to efficient in-hospital trauma triage by reducing the amount of resources required and by improving health

outcomes. This study evaluates current practice of trauma team activation (TTA) in Dutch emergency departments (EDs).
Methods: A survey was conducted among managers of all 102 EDs in the Netherlands, using a semi-structured online questionnaire.
Results: Seventy-two questionnaires were analysed. Most EDs use a one-team system (68 %). EDs with a tiered-response receive more multi trauma patients ($p < 0.01$) and have more trauma team alerts per year ($p < 0.05$) than one-team EDs. The number of trauma team members varies from three to 16 professionals. The ED nurse usually receives the pre-notification (97 %), whereas the decision to activate a team is made by an ED nurse (46 %), ED physician (30 %), by multiple professionals (20 %) or other (4 %). Information in the pre-notification mostly used for trauma team activation are Airway-Breathing-Circulation (87 %), Glasgow Coma Score (90 %), and Revised Trauma Score (85 %) or Paediatric Trauma Score (86 %). However, this information is only available for 75 % of the patients or less. Only 56 % of the respondents were satisfied with their current in-hospital trauma triage system.
Conclusions: Trauma team activation varies across Dutch EDs and there is room for improvement in the trauma triage system used, size of the teams and the professionals involved. More direct communication and more uniform criteria could be used to efficiently and safely activate a specific trauma team. Therefore, the implementation of a revised national consensus guideline is recommended.

Gepubliceerd: Scand J Trauma Resusc Emerg Med 2015;23(1):100
Impact factor: 2.025

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8. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands
Elferink MA, de Jong KP, Klaase JM, Siemerink EJ, de Wilt JH

Purpose: The main cause of death of colorectal cancer patients is metastatic disease. Approximately 20-25 % of the patients present with metastases at time of diagnosis. The clinical course of patients who develop metachronous metastases, however, is less clear. The aims of this study were to describe the incidence, treatment and survival of patients with metachronous metastases from colorectal cancer and to determine risk factors for developing metachronous metastases.
Methods: From the Netherlands Cancer Registry, patients diagnosed with colorectal carcinoma in the period 2002-2003 in North-East Netherlands were selected. Patients were followed for 5 years after diagnosis of the primary tumour. Kaplan-Meier method and Cox regression analyses were used to determine predictors for developing metastases and to analyse overall survival.
Results: In total, 333 of 1743 (19 %) patients developed metachronous metastases. The majority (83 %) of these metastases were diagnosed within 3 years, and the most frequent site was the liver. Patients with advanced stage and patients with tumours in the descending colon or in the rectum were more likely to develop metastases. Approximately 10 % of all patients underwent intentionally curative treatment for their metastases, with a 5-year survival rate of 60 %. Treatment of

metastases and pathologic N (pN) status were independent prognostic factors for overall survival.
Conclusions: Site and stage of the primary tumour were predictors for developing metachronous metastases. A limited number of patients with metastatic disease were treated with a curative intent. These patients had a good prognosis. Therefore, focus should be on identifying more patients who could benefit from curative treatment.

Gepubliceerd: Int J Colorectal Dis 2015;30(2):205-12
Impact factor: 2.449

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9. Preference for endovascular aortic aneurysm repair: results of RCTs versus nationwide audits
Geelkerken RH, Hamming JF

This short comment puts into perspective the value of randomised controlled clinical trials in comparison with nationwide audits in the field of aortic aneurysm treatment. RCTs represent greater scientific value but nationwide audits represent daily practices and seem to be more appropriate for shared decision-making.

Gepubliceerd: Ned Tijdschr Geneeskd 2015;160:A9290
Impact factor: 0

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10. A woman with a symptomatic abdominal swelling
Gray SA, Raber MH, Klaase JM

A 51-year-old woman visited the surgery outpatient clinic with an abdominal swelling. The swelling had become larger over the past few years and caused mechanical complaints. With MRI a liver cyst measuring 14 x 11 cm was diagnosed. The patient underwent laparoscopic deroofing of the liver cyst.

Gepubliceerd: Ned Tijdschr Geneeskd 2015;159(0):A8732
Impact factor: 0

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11. Colorectal Liver Metastasis, Primary Gallbladder Carcinoma and Myelofibrosis Present Simultaneously in a Liver Resection Specimen
Gray SA, Raber MH, Provoost E, Toes GJ, Klaase JM

Myelofibrosis and gallbladder carcinoma are both very rare diseases. This case report describes a patient with a history of myelofibrosis and colorectal carcinoma who was diagnosed with colorectal liver metastases. Surgery was performed to remove the metastases, and on site, the gallbladder was removed because of involvement in one of the liver lesions. After pathological examination, a primary gallbladder carcinoma and myelofibrosis were found in addition to the liver

metastases. The combination of diseases was not likely to be interconnected but rather an unlucky course of events for the patient.

Gepubliceerd: Case Rep Gastroenterol 2015 Sep;9(3):335-40
Impact factor: 0

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12. Photoacoustic image patterns of breast carcinoma and comparisons with Magnetic Resonance Imaging and vascular stained histopathology
Heijblom M, Piras D, Brinkhuis M, van Hespen JC, van den Engh FM, van der Schaaf M, Klaase JM, van Leeuwen TG, Steenbergen W, Manohar S

Photoacoustic (optoacoustic) imaging can visualize vasculature deep in tissue using the high contrast of hemoglobin to light, with the high-resolution possible with ultrasound detection. Since angiogenesis, one of the hallmarks of cancer, leads to increased vascularity, photoacoustics holds promise in imaging breast cancer as shown in proof-of-principle studies. Here for the first time, we investigate if there are specific photoacoustic appearances of breast malignancies which can be related to the tumor vascularity, using an upgraded research imaging system, the Twente Photoacoustic Mammoscope. In addition to comparisons with x-ray and ultrasound images, in subsets of cases the photoacoustic images were compared with MR images, and with vascular staining in histopathology. We were able to identify lesions in suspect breasts at the expected locations in 28 of 29 cases. We discovered generally three types of photoacoustic appearances reminiscent of contrast enhancement types reported in MR imaging of breast malignancies, and first insights were gained into the relationship with tumor vascularity.

Gepubliceerd: Sci Rep 2015;5:11778
Impact factor: 5.578

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13. Long Term Results of Kissing Stents in the Aortic Bifurcation
Hinnen JW, Konickx MA, Meerwaldt R, Kolkert JL, van der Palen J, Huisman AB, Geelkerken RH

Background: To evaluate the long-term outcome after aortoiliac kissing stent placement and to analyze variables, which potentially influence the outcome of endovascular reconstruction of the aortic bifurcation.
Methods: All patients treated with aortoiliac kissing stents at our institution between April 1995 and August 2011 were retrospectively identified from a prospective single-center database. Data regarding patient characteristics (age, gender, smoking, cardio- and cerebrovascular risk factors, hyperlipidaemia, diabetes mellitus and use of antihypertensive medication), symptoms, pre-interventional examination and imaging, procedural details and follow-up were retrieved. Patency rates were calculated with Kaplan-Meier analysis. Factors affecting the patency were determined with Cox uni- and multivariate analysis.
Results: A total of 215 patients (63% men, mean age 61 +/- 10 years) were included. The median follow-up period was 31 (IQR 47.1) months. Primary, primary

assisted, and secondary patency rates were 97%, 97%, and 99%, respectively, at one month; 92%, 95% and 94% at four months; 75%, 86%, and 91% at two years; 70%, 81%, and 91% at 5 years; and 67%, 81%, and 91% at ten years. Younger age and previous aortoiliac treatment were predictors for reduced primary and primary assisted patency. Smoking, previous aortoiliac intervention, TASC C and D lesions were predictors for reduced secondary patency.
Conclusions: Reconstruction of the aortoiliac bifurcation with kissing stents is feasible, safe and effective in all types of lesions with satisfying long term patencies. TASC C and D lesions are associated with a higher occlusion rate. Younger age and previous aortoiliac interventions are predictors for reduced primary and primary assisted patency.

Gepubliceerd: Acta Chir Belg 2015 May;115(3):191-7
Impact factor: 0.408

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14. Endarterectomy or carotid artery stenting: the quest continues part two
Kolkert JL, Meerwaldt R, Geelkerken RH, Zeebregts CJ

Background: Although randomized trials on carotid artery stenting (CAS) could not establish its equivalence to carotid endarterectomy (CEA) in patients with symptomatic carotid disease, CAS is rapidly evolving. Data on long-term outcome after CAS from randomized trials have now become available and ongoing, prospectively held registries frequently publish their results in increasing numbers of patients. We have therefore reviewed the currently available literature and provide an update of our previous article on this topic.
Data sources: PubMed literature searches were performed to identify relevant studies regarding current status of CEA and stenting for symptomatic carotid stenosis.
Conclusions: The efficacy of CAS in patients with symptomatic carotid artery stenosis remains unclear because of varying results in randomized trials. Although multiple registries do report promising results after CAS, peri-interventional stroke/death rates still exceed those rates currently found after CEA. Therefore, CEA remains the "gold standard" in treating these patients.

Gepubliceerd: Am J Surg 2015;209(2):403-12
Impact factor: 2.291

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15. Prospective multicentre cohort study of patient-reported outcomes after cholecystectomy for uncomplicated symptomatic cholecystolithiasis
Lamberts MP, Den Oudsten BL, Gerritsen JJ, Roukema JA, Westert GP, Drenth JP, van Laarhoven CJ

Background: Up to 33 per cent of patients with uncomplicated symptomatic cholecystolithiasis report persistent pain after cholecystectomy. The aim of this study was to determine characteristics associated with patient-reported absence of

abdominal pain after cholecystectomy, improved abdominal symptoms, and patient-reported positive cholecystectomy results in a prospective cohort multicentre study.
Methods: Patients aged 18 years or more with symptomatic cholecystolithiasis who had a cholecystectomy between June 2012 and June 2014 in one of three hospitals were included. Before surgery all patients were sent the Gastrointestinal Quality of Life Index (GIQLI) questionnaire and the McGill Pain Questionnaire (MPQ). At 12 weeks after surgery, patients were invited to complete the GIQLI and Patients' Experience of Surgery Questionnaire (PESQ). Logistic regression analyses were performed to determine associations.
Results: Questionnaires were sent to 552 patients and returned by 342 before and after surgery. Postoperative absence of abdominal pain was reported by 60.5 per cent of patients. A high preoperative GIQLI score, episodic pain, and duration of pain of 1 year or less were associated with postoperative absence of pain. These factors showed no association with improved abdominal symptoms (reported by 91.5 per cent of patients) or a positive surgery result (reported by 92.4 per cent).
Conclusion: Preoperative characteristics determine the odds for relief of abdominal pain after cholecystectomy. However, these factors were not associated with patient-reported improvement of abdominal symptoms or patient-reported positive cholecystectomy results, highlighting the variation of internal standards and expectations of patients before cholecystectomy.

Gepubliceerd: Br J Surg 2015 Jul 22;102(11):1402-9
Impact factor: 5.542

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16. Successful treatment of fulminant postoperative bleeding due to acquired haemophilia
Mekenkamp LJ, Beishuizen A, Slomp J, Legdeur MC, Klaase JM, Trof RJ

Acquired haemophilia is a rare but life-threatening phenomenon in patients who have undergone surgical treatment. We describe a patient with a history of pancreatic cancer and a conventional pancreaticoduodenectomy, who underwent elective resection of an enterocutaneous fistula, complicated by fulminant haemorrhagic shock, caused by acquired haemophilia A. Eventually, the bleeding was controlled by a combination of aggressive haemostatic and immunosuppressive therapy. Prompt diagnosis of acquired haemophilia is crucial to allow early and appropriate haemostatic treatment and reduce the period of increased bleeding risk by eradicating the inhibitor with immunosuppressive therapy.

Gepubliceerd: Neth J Med 2015 May;73(4):182-6
Impact factor: 1.969

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17. Pain Management in the Emergency Chain: The Use and Effectiveness of Pain Management in Patients With Acute Musculoskeletal Pain
Pierik JG, IJzerman MJ, Gaakeer MI, Berben SA, van Eenennaam FL, van Vugt AB, Doggen CJ

Objective: While acute musculoskeletal pain is a frequent complaint in emergency care, its management is often neglected, placing patients at risk for insufficient pain relief. Our aim is to investigate how often pain management is provided in the prehospital phase and emergency department (ED) and how this affects pain relief. A secondary goal is to identify prognostic factors for clinically relevant pain relief.
Design: This prospective study (PROTACT) includes 697 patients admitted to ED with musculoskeletal extremity injury. Data regarding pain, injury, and pain management were collected using questionnaires and registries.
Results: Although 39.9% of the patients used analgesics in the prehospital phase, most patients arrived at the ED with severe pain. Despite the high pain prevalence in the ED, only 35.7% of the patients received analgesics and 12.5% received adequate analgesic pain management. More than two-third of the patients still had moderate to severe pain at discharge. Clinically relevant pain relief was achieved in only 19.7% of the patients. Pain relief in the ED was higher in patients who received analgesics compared with those who did not. Besides analgesics, the type of injury and pain intensity on admission were associated with pain relief.
Conclusions: There is still room for improvement of musculoskeletal pain management in the chain of emergency care. A high percentage of patients were discharged with unacceptable pain levels. The use of multimodal pain management or the implementation of a pain management protocol might be useful methods to optimize pain relief. Additional research in these areas is needed.

Gepubliceerd: Pain Med 2015;16(5):970-84
Impact factor: 2.339

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18. Pre-operative sentinel lymph node localization in breast cancer with superparamagnetic iron oxide MRI: the SentiMAG Multicentre Trial imaging subprotocol

Pouw JJ, Grootendorst MR, Bezooijen R, Klazen CA, De Bruin WI, Klaase JM, Hall-Craggs MA, Douek M, Ten Haken B

Objective: Sentinel lymph node biopsy (SLNB) with a superparamagnetic iron oxide (SPIO) tracer was shown to be non-inferior to the standard combined technique in the SentiMAG Multicentre Trial. The MRI subprotocol of this trial aimed to develop a magnetic alternative for pre-operative lymphoscintigraphy (LS). We evaluated the feasibility of using MRI following the administration of magnetic tracer for pre-operative localization of sentinel lymph nodes (SLNs) and its potential for non-invasive identification of lymph node (LN) metastases.
Methods: Patients with breast cancer scheduled to undergo SLNB were recruited for pre-operative LS, single photon emission CT (SPECT)-CT and SPIO MRI. T1 weighted turbo spin echo and T2 weighted gradient echo sequences were used before and after interstitial injection of magnetic tracer into the breast. SLNs on MRI were defined as LNs with signal drop and direct lymphatic drainage from the injection site. LNs showing inhomogeneous SPIO uptake were classified as metastatic. During surgery, a handheld magnetometer was used for SLNB. Blue or radioactive nodes were also excised. The number of SLNs and MR assessment of metastatic involvement were compared with surgical and histological outcomes.

Results: 11 patients were recruited. SPIO MRI successfully identified SLNs in 10 of 11 patients vs 11 of 11 patients with LS/SPECT-CT. One patient had metastatic involvement of four LNs, and this was identified in one node on pre-operative MRI.
Conclusion: SPIO MRI is a feasible technique for pre-operative localization of SLNs and, in combination with intraoperative use of a handheld magnetometer, provides an entirely radioisotope-free technique for SLNB. Further research is needed for the evaluation of MRI characterization of LN involvement using subcutaneous injection of magnetic tracer.
Advances in knowledge: This study is the first to demonstrate that an interstitially administered magnetic tracer can be used both for pre-operative imaging and intraoperative SLNB, with equal performance to imaging and localization with radioisotopes.

Gepubliceerd: Br J Radiol 2015 Dec;88(1056):20150634
Impact factor: 2.026

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19. Beneficial Effects of Pre-operative Exercise Therapy in Patients with an Abdominal Aortic Aneurysm: A Systematic Review
Pouwels S, Willigendael EM, van Sambeek MR, Nienhuijs SW, Cuypers PW, Teijink JA

Objective/Background: The impact of post-operative complications in abdominal aortic aneurysm (AAA) surgery is substantial, and increases with age and concomitant co-morbidities. This systematic review focuses on the possible effects of pre-operative exercise therapy (PET) in patients with AAA on post-operative complications,aerobic capacity, physical fitness, and recovery.
Methods: A systematic search on PET prior to AAA surgery was conducted. The methodological quality of the included studies was rated using the Physiotherapy Evidence Database scale. The agreement between the reviewers was assessed with Cohen's kappa.
Results: Five studies were included, with a methodological quality ranging from moderate to good. Cohen's kappa was 0.79. Three studies focused on patients with an AAA (without indication for surgical repair) with physical fitness as the outcome measure. One study focused on PET in patients awaiting AAA surgery and one study focused on the effects of PET on post-operative complications, length of stay, and recovery.
Conclusion: PET has beneficial effects on various physical fitness variables of patients with an AAA. Whether this leads to less complications or faster recovery remains unclear. In view of the large impact of post-operative complications, it is valuable to explore the possible benefits of a PET program in AAA surgery.

Gepubliceerd: Eur J Vasc Endovasc Surg 2015 Jan;49(1):66-76
Impact factor: 2.490

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20. Assessment of infection in chronic wounds based on the monitoring of elastase, lysozyme and myeloperoxidase activities

Schiffer D, Blokhuis-Arkes M, van der Palen J, Sigl E, Heinzle A, Guebitz GM

Infection in wounds affects about 2% of the population in developed countires at least once in their lifetime, and the lack of tools for its rapid diagnosis is still a problem 1 . Standard procedures of infection detection include the judgement of the classical clinical signs, the detection of signals specific to secondary wounds, or the quantification of the microbial load 2-5 . The determination of the microbial load is a time-consuming standard procedure, although the presence of microbes per se is not indicative of infection 2 . This article is protected by copyright. All rights reserved.

Gepubliceerd: Br J Dermatol 2015 May 12;173(6):1529-31
Impact factor: 4.275

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21. The Preoperative CT Scan Can Help to Predict Postoperative Complications after Pancreatoduodenectomy
Schroder FF, de Graaff F, Bouman DE, Brusse-Keizer M, Slump KH, Klaase JM

After pancreatoduodenectomy, complication rates are up to 40%. To predict the risk of developing postoperative pancreatic fistula or severe complications, various factors were evaluated. 110 consecutive patients undergoing pancreatoduodenectomy at our institute between January 2012 and September 2014 with complete CT scan were retrospectively identified. Pre-, per-, and postoperative patients and pathological information were gathered. The CT scans were analysed for the diameter of the pancreatic duct, attenuation of the pancreas, and the visceral fat area. All data was statistically analysed for predicting POPF and severe complications by univariate and multivariate logistic regression analyses. The POPF rate was 18%. The VFA measured at umbilicus (OR 1.01; 95% CI = 1.00-1.02; P = 0.011) was an independent predictor for POPF. The severe complications rate was 33%. Independent predictors were BMI (OR 1.24; 95% CI = 1.10-1.42; P = 0.001), ASA class III (OR 17.10; 95% CI = 1.60-182.88; P = 0.019), and mean HU (OR 0.98; 95% CI = 0.96-1.00; P = 0.024). In conclusion, VFA measured at the umbilicus seems to be the best predictor for POPF. BMI, ASA III, and the mean HU of the pancreatic body are independent predictors for severe complications following PD.

Gepubliceerd: Biomed Res Int 2015;2015:824525
Impact factor: 1.579

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22. Common Iliac Artery Aneurysm Repair Using a Sac-Anchoring Endograft to Preserve the Internal Iliac Artery
Ter Mors TG, van Sterkenburg SM, van den Ham LH, Reijnen MM

Purpose: To report the application of the Nellix endovascular aneurysm sealing system to successfully treat a unilateral common iliac aneurysm and preserve the internal iliac artery.

Case report: An 85-year-old man presented with right-sided necrosis of the third and fourth toe. Computed tomography angiography (CTA) showed a right 40-mm popliteal aneurysm and a 38-mm left fusiform common iliac artery aneurysm. After endovascular exclusion of the popliteal aneurysm, the Nellix device was positioned to exclude the common iliac artery aneurysm while preserving the internal iliac artery. Postoperative CTA showed no endoleak and a patent internal iliac artery. At 1 year, duplex ultrasound documented a common iliac aneurysm diameter of 32 mm without complications.
Conclusion: Endovascular sealing using the Nellix device can be applied to exclude selected common iliac artery aneurysms with an adequate length and a minimal distal neck, with preservation of the internal iliac artery. The endobag can be positioned such that the aneurysm is completely excluded while the orifice of the side branch is not endangered.

Gepubliceerd: J Endovasc Ther 2015 Oct 5;22(6):886-8
Impact factor: 3.353

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23. Late Conversion After Sac Anchoring Endoprosthesis for Secondary Aortic Aneurysm Infection
Tolenaar JL, van den Ham LH, Reijnen MM, de Vries JP

Purpose: To demonstrate explantation of the Nellix Endovascular Aneurysm Sealing (EVAS) System in the setting of infection.
Case reports: Two male patients, 71 and 83 years old, underwent Nellix implantation for asymptomatic infrarenal aortic aneurysms measuring 5.1 and 6.3 cm, respectively. Each developed late infections at 8 and 4 months post EVAS, respectively. The first patient experienced aneurysm rupture after medical therapy failed; the Nellix endosystem was explanted in an uneventful procedure. The second patient developed an aortoduodenal fistula, which was sutured before the Nellix device was removed without complications. The patient died 3 months later, presumably due to ongoing infection.
Conclusion: The need to explant a Nellix EVAS System due to graft infection is a straightforward procedure compared to the removal of a conventional endograft with suprarenal fixation. It requires only temporary suprarenal clamping. The devices can be easily removed due to the lack of penetrating components and without damage to the aortic segment needed to create an anastomosis.

Gepubliceerd: J Endovasc Ther 2015 Oct;22(5):813-8
Impact factor: 3.353

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24. Circulating tumor cells before and during follow-up after breast cancer surgery
van Dalum G, van der Stam GJ, Tibbe AG, Franken B, Mastboom WJ, Vermes I, de Groot MR, Terstappen LW

The presence of circulating tumor cells (CTC) is an independent prognostic factor for progression-free and overall survival for patients with metastatic and newly diagnosed breast cancer. The present study was undertaken to explore whether the presence of CTC before and during follow-up after surgery is associated with recurrence free survival (RFS) and overall survival (OS). In a prospective single center study, CTC were enumerated with the CellSearch system in 30 ml of peripheral blood of 403 stage I-III patients before undergoing surgery for breast cancer (A) and if available 1 week after surgery (B), after adjuvant chemo- and/or radiotherapy or before start of long-term hormonal therapy (C), one (D), two (E) and three (F) years after surgery. Patients were stratified into unfavorable (CTC >/=1) and favorable (CTC=0) prognostic groups. >1 CTC in 30 ml blood was detected in 75/403 (19%) at A, 66/367 (18%) at B, 40/263 (15%) at C, 30/235 (12%) at D, 18/144 (11%) at E and 11/83 (13%) at F. RFS and OS was significantly lower for unfavorable CTC as compared to favorable CTC before surgery (p=0.022 and p=0.006), after adjuvant therapy (p<0.001 and p=0.018) and one (p=0.006 and p=0.013) and two (p<0.001 and p=0.045) years after surgery, but not 1 week post-surgery. The presence of CTC in blood drawn pre and one and two years after surgery, but not post-surgery is associated with shorter RFS and OS for stage I-III breast cancer.

Gepubliceerd: Int J Oncol 2015 Oct 6;46(1):407-13
Impact factor: 3.025

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25. Importance of circulating tumor cells in newly diagnosed colorectal cancer
van Dalum G, Stam GJ, Scholten LF, Mastboom WJ, Vermes I, Tibbe AG, de Groot MR, Terstappen LW

Presence of circulating tumor cells (CTC) is associated with poor prognosis in patients with metastatic colorectal cancer (CRC). The present study was conducted to determine if the presence of CTC prior to surgery and during followup in patients with newly diagnosed non-metastatic CRC can identify patients at risk for disease recurrence. In a prospective single center study 183 patients with newly diagnosed non-disseminated CRC, scheduled for surgery, were enrolled and followed-up for a median of 5.1 years. CTC were enumerated with the CellSearch system in 4 aliquots of 7.5 ml of blood before surgery and at several time-points during follow-up after surgery. The results showed that >/=1 CTC/30 ml of blood were detected in 44 (24%) patients before surgery. Patients with CTC before surgery had a significant decrease in recurrence-free survival (RFS, log-rank test p=0.014) and colon cancer related survival (CCRS, p=0.002). The 5-year RFS dropped from 75 to 61% and the 5-year CCRS from 83 to 69% for patients with CTC before surgery. The presence of CTC and positive lymph nodes remained significant factors in multivariate analysis for recurrence-free survival (RFS). Surprisingly, the presence of CTC weeks after surgery was not significantly associated with RFS and CCRD whereas CTC 2-3 years after surgery was again significantly associated with RFS and CCRD. The presence of CTC in patients with stage I-III CRC before surgery is associated with a significant reduction in RFS and CCRS. These findings suggest a role of CTC detection to assess which patients need adjuvant treatment.

Gepubliceerd: Int J Oncol 2015 Mar;46(3):1361-8
Impact factor: 3.025

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26. Abdominal Aortic Aneurysm Repair Using Nellix EndoVascular Aneurysm Sealing
van den Ham LH, Zeebregts CJ, de Vries JP, Reijnen MM

Since the dawn of endovascular aortic aneurysm repair (EVAR), starting from its initial report in 1991, there has been a significant evolution in stent graft design and delivery systems. Complications, mostly endoleaks, and re-intervention rates after EVAR remain amongst the most challenging aspects in comparison with traditional open repair. The use of a sac-anchoring endograft changes the approach of aneurysm exclusion. The Nellix EndoVascular Aneurysm Sealing system (Endologix Inc., Irvine, CA) consists of balloon expandable stents surrounded by endobags that are filled with a polymer thereby sealing the aneurysm. By sealing the aneurysm sac instead of exclusion with only proximal and distal fixation, the risk of stent migration and endoleaks is theoretically diminished. Current investigational use is aimed to confirm clinical success, decreased complication, and secondary intervention rates compared to conventional endovascular repair.

Gepubliceerd: Surg Technol Int 2015 May;26:226-31
Impact factor: 0

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27. Long-term effects of a regional care pathway for patients with rectal cancer
van Hoeve JC, Elferink MA, Klaase JM, Kouwenhoven EA, Schiphorst PP, Siesling S

Purpose: Introducing care pathways is seen as a method to realise patient-focussed care conform evidence-based guidelines. The goal of this study is to determine the long-term effects of a regional care pathway for patients with rectal cancer.
Patients and Methods: Data on almost 400 patients with rectal carcinoma from three hospitals were obtained from the Netherlands Cancer Registry and the Dutch Surgical Colorectal Audit. Results on seven structure and process indicators were analysed and compared before and at two time points after implementing a regional care pathway over a total period from 2007 to 2012. To determine motivation and interpret the results, relevant professionals of the participating hospitals were interviewed.
Results: After implementing the care pathway, the performance of computed tomography (CT) scans in the diagnostic phase significantly improved ($p = 0.007/0.07$). The number of patients discussed in the preoperative multidisciplinary team (MDT) meeting improved significantly ($p = <0.001$), and after implementing the care pathway, 94 % of the patients were discussed. Further, a significant reduction in time between the first tumour biopsy and the MDT meeting was realised ($p = 0.01$). Professionals stated that the regional care pathway has led to more clarity

about the patient route and more awareness about complying with evidence-based guidelines.
Conclusions: The regional care pathway provided a solid basis for uniforming care, working according evidence-based guidelines and further cooperation on regional level. For mainly the waiting and throughput times, the guidelines and norms had probably a stronger effect on the results than the care pathway.

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Impact factor: 2.449

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28. Laparoscopic peritoneal lavage or sigmoidectomy for perforated diverticulitis with purulent peritonitis: a multicentre, parallel-group, randomised, open-label trial
Vennix S, Musters GD, Mulder IM, Swank HA, Consten EC, Belgers EH, van Geloven AA, Gerhards MF, Govaert MJ, van Grevenstein WM, Hoofwijk AG, Kruyt PM, Nienhuijs SW, Boermeester MA, Vermeulen J, van Dieren S, Lange JF, Bemelman WA, Ladies trial collaborators,includes van Duyn EB and Klaase JM

Background: Case series suggest that laparoscopic peritoneal lavage might be a promising alternative to sigmoidectomy in patients with perforated diverticulitis. We aimed to assess the superiority of laparoscopic lavage compared with sigmoidectomy in patients with purulent perforated diverticulitis, with respect to overall long-term morbidity and mortality.
Methods: We did a multicentre, parallel-group, randomised, open-label trial in 34 teaching hospitals and eight academic hospitals in Belgium, Italy, and the Netherlands (the Ladies trial). The Ladies trial is split into two groups: the LOLA group comparing laparoscopic lavage with sigmoidectomy and the DIVA group comparing Hartmann's procedure with sigmoidectomy plus primary anastomosis. The DIVA section of this trial is still underway but here we report the results of the LOLA section. Patients with purulent perforated diverticulitis were enrolled for LOLA, excluding patients with faecal peritonitis, aged older than 85 years, with high-dose steroid use (>/=20 mg daily), and haemodynamic instability. Patients were randomly assigned (2:1:1; stratified by age [<60 years vs >/=60 years]) using secure online computer randomisation to laparoscopic lavage, Hartmann's procedure, or primary anastomosis in a parallel design after diagnostic laparoscopy. Patients were analysed according to a modified intention-to-treat principle and were followed up after the index operation at least once in the outpatient setting and after sigmoidoscopy and stoma reversal, according to local protocols. The primary endpoint was a composite endpoint of major morbidity and mortality within 12 months. This trial is registered with ClinicalTrials.gov, number NCT01317485.
Findings: Between July 1, 2010, and Feb 22, 2013, 90 patients were randomly assigned in the LOLA section of the Ladies trial when the study was terminated by the data and safety monitoring board because of an increased event rate in the lavage group. Two patients were excluded for protocol violations. The primary endpoint occurred in 30 (67%) of 45 patients in the lavage group and 25 (60%) of 42 patients in the sigmoidectomy group (odds ratio 1.28, 95% CI 0.54-3.03, p=0.58). By

12 months, four patients had died after lavage and six patients had died after sigmoidectomy (p=0.43).
Interpretation: Laparoscopic lavage is not superior to sigmoidectomy for the treatment of purulent perforated diverticulitis.
Funding: Netherlands Organisation for Health Research and Development.

Lancet 2015 Sep 26;386(10000):1269-77
Impact factor: 45.217

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29. Intensified follow-up in colorectal cancer patients using frequent Carcino-Embryonic Antigen (CEA) measurements and CEA-triggered imaging: Results of the randomized "CEAwatch" trial
Verberne CJ, Zhan Z, van den Heuvel E, Grossmann I, Doornbos PM, Havenga K, Manusama E, Klaase J, van der Mijle HC, Lamme B, Bosscha K, Baas P, van Ooijen B, Nieuwenhuijzen G, Marinelli A, van der Zaag E, Wasowicz D, de Bock GH, Wiggers T

Aim: The value of frequent Carcino-Embryonic Antigen (CEA) measurements and CEA-triggered imaging for detecting recurrent disease in colorectal cancer (CRC) patients was investigated in search for an evidence-based follow-up protocol.
Methods: This is a randomized-controlled multicenter prospective study using a stepped-wedge cluster design. From October 2010 to October 2012, surgically treated non-metastasized CRC patients in follow-up were followed in eleven hospitals. Clusters of hospitals sequentially changed their usual follow-up care into an intensified follow-up schedule consisting of CEA measurements every two months, with imaging in case of two CEA rises. The primary outcome measures were the proportion of recurrences that could be treated with curative intent, recurrences with definitive curative treatment outcome, and the time to detection of recurrent disease.
Results: 3223 patients were included; 243 recurrences were detected (7.5%). A higher proportion of recurrences was detected in the intervention protocol compared to the control protocol (OR = 1.80; 95%-CI: 1.33-2.50; p = 0.0004). The proportion of recurrences that could be treated with curative intent was higher in the intervention protocol (OR = 2.84; 95%-CI: 1.38-5.86; p = 0.0048) and the proportion of recurrences with definitive curative treatment outcome was also higher (OR = 3.12, 95%-CI: 1.25-6.02, p-value: 0.0145). The time to detection of recurrent disease was significantly shorter in the intensified follow-up protocol (HR = 1.45; 95%-CI: 1.08-1.95; p = 0.013).
Conclusion: The CEAwatch protocol detects recurrent disease after colorectal cancer earlier, in a phase that a significantly higher proportion of recurrences can be treated with curative intent.

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Impact factor: 3.009

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30. Arterial clamping leads to stenosis at clamp sites after femoropopliteal bypass surgery
Vriens BH, Pol RA, Hulsebos RG, van Det RJ, van der Palen J, Zeebregts CJ, Geelkerken RH

Background: To date, the incidence and clinical relevance of arterial stenosis at clamp sites after femoropopliteal bypass surgery is unknown.
Methods: Ninety-four patients underwent a femoropopliteal bypass in which the arterial inflow and outflow clamp sites were controlled by the Fogarty-Soft-Inlay clamp and marked with an hemoclip. The number of pre-existing atherosclerotic segments, clamp force, and clamp time were recorded and the occurrence of a stenosis at the clamp site was determined.
Results: After a mean follow-up of 83 months, a significant stenosis was confirmed at 23 of the 178 clamp sites (12.9%; 95% confidence interval 8.4 to 18.8). The mean number of pre-existing atherosclerotic segments (P = .28) and the mean clamp force (P = .55) was similar between the groups with and without a stenosis. There was a significant difference regarding clamp time between the group with and without a stenosis (38 minutes and 26 minutes, P = .001).
Conclusion: Arterial clamping, even with the Fogarty-Soft-Inlay clamp, can lead to clamp stenosis and seems to be related to the duration of clamping, but not to pre-existent atherosclerotic burden.

Gepubliceerd: Am J Surg 2015 May 7;210(3):536-44
Impact factor: 2.291

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31. Personalisation of breast cancer follow-up: a time-dependent prognostic nomogram for the estimation of annual risk of locoregional recurrence in early breast cancer patients
Witteveen A, Vliegen IM, Sonke GS, Klaase JM, IJzerman MJ, Siesling S

The objective of this study was to develop and validate a time-dependent logistic regression model for prediction of locoregional recurrence (LRR) of breast cancer and a web-based nomogram for clinical decision support. Women first diagnosed with early breast cancer between 2003 and 2006 in all Dutch hospitals were selected from the Netherlands Cancer Registry (n = 37,230). In the first 5 years following primary breast cancer treatment, 950 (2.6 %) patients developed a LRR as first event. Risk factors were determined using logistic regression and the risks were calculated per year, conditional on not being diagnosed with recurrence in the previous year. Discrimination and calibration were assessed. Bootstrapping was used for internal validation. Data on primary tumours diagnosed between 2007 and 2008 in 43 Dutch hospitals were used for external validation of the performance of the nomogram (n = 12,308). The final model included the variables grade, size, multifocality, and nodal involvement of the primary tumour, and whether patients were treated with radio-, chemo- or hormone therapy. The index cohort showed an area under the ROC curve of 0.84, 0.77, 0.70, 0.73 and 0.62, respectively, per subsequent year after primary treatment. Model predictions were well calibrated. Estimates in the validation cohort did not differ significantly from the index cohort.

The results were incorporated in a web-based nomogram (http://www.utwente.nl/mira/influence). This validated nomogram can be used as an instrument to identify patients with a low or high risk of LRR who might benefit from a less or more intensive follow-up after breast cancer and to aid clinical decision making for personalised follow-up.

Gepubliceerd: Breast Cancer Res Treat 2015 Jul 11;152(3):627-36
Impact factor: 3.940

Totale impact factor: 178.393
Gemiddelde impact factor: 5.755

Aantal artikelen 1e, 2e of laatste auteur: 15
Totale impact factor: 24.467
Gemiddelde impact factor: 1.631

Intensive Care

1. Reply to GC Ligthart-Melis et al
Buijs N, Brinkmann SJ, Oosterink JE, Luttikhold J, Schierbeek H, Wisselink W, Beishuizen A, van Goudoever JB, Houdijk AP, van Leeuwen PA, Vermeulen MA

Gepubliceerd: Am J Clin Nutr 2015 Apr;101(4):892-3
Impact factor: 6.770

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2. Diminished adrenal sensitivity to endogenous and exogenous adrenocorticotropic hormone in critical illness: a prospective cohort study
de Jong MF, Molenaar N, Beishuizen A, Groeneveld ABJ

Introduction: Adrenal dysfunction may represent critical illness-related corticosteroid insufficiency (CIRCI), as evidenced by a diminished cortisol response to exogenous adrenocorticotropic hormone (ACTH), but this concept and its clinical significance remain highly controversial. We studied the adrenal response to exogenous ACTH as a function of the endogenous cortisol-to-ACTH ratio, a measure of adrenal sensitivity, and of clinical variables, during critical illness and recovery from the acute phase.
Methods: We prospectively included 59 consecutive septic and nonseptic patients in the intensive care unit with treatment-insensitive hypotension in whom CIRCI was suspected; patients having received etomidate and prolonged corticosteroids were excluded. An ACTH test (250 mug) was performed, followed by a second test after >/=7 days in acute-phase survivors. Serum total and free cortisol, ACTH, and clinical variables were assessed. Patients were divided according to responses (delta, Delta) of cortisol to ACTH at the first and second tests.
Results: Patients with low (<250 nM) Delta cortisol (n = 14 to 17) had higher baseline cortisol and ACTH but lower cortisol/ACTH ratios than patients with a normal Delta cortisol (>/=250 nM) in the course of time. A low Delta cortisol in time was associated with more-severe disease, culture-positive sepsis, and prolonged activated prothrombin time. Results for free cortisol were similar.
Conclusions: Even though the pituitary-adrenal axis is activated after stress during critical illness, diminished adrenal sensitivity to endogenous ACTH predicts a low increase of cortisol to exogenous ACTH, suggesting adrenal dysfunction, irrespective of the stage of disease. The data further suggest a role of disease severity and culture-positive sepsis.

Gepubliceerd: Crit Care 2015;19:1
Impact factor: 4.476

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3. Erratum to: Diminished adrenal sensitivity to endogenous and exogenous adrenocorticotropic hormone in critical illness: a prospective cohort study
de Jong MF, Molenaar N, Beishuizen A, Groeneveld AB

Gepubliceerd: Crit Care 2015;19(1):313
Impact factor: 4.476

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4. Early EEG contributes to multimodal outcome prediction of postanoxic coma
Hofmeijer J, Beernink TM, Bosch FH, Beishuizen A, Tjepkema-Cloostermans MC, van Putten MJ

Objectives: Early identification of potential recovery of postanoxic coma is a major challenge. We studied the additional predictive value of EEG.
Methods: Two hundred seventy-seven consecutive comatose patients after cardiac arrest were included in a prospective cohort study on 2 intensive care units. Continuous EEG was measured during the first 3 days. EEGs were classified as unfavorable (isoelectric, low-voltage, burst-suppression with identical bursts), intermediate, or favorable (continuous patterns), at 12, 24, 48, and 72 hours. Outcome was dichotomized as good or poor. Resuscitation, demographic, clinical, somatosensory evoked potential, and EEG measures were related to outcome at 6 months using logistic regression analysis. Analyses of diagnostic accuracy included receiver operating characteristics and calculation of predictive values.
Results: Poor outcome occurred in 149 patients (54%). Single measures unequivocally predicting poor outcome were an unfavorable EEG pattern at 24 hours, absent pupillary light responses at 48 hours, and absent somatosensory evoked potentials at 72 hours. Together, these had a specificity of 100% and a sensitivity of 50%. For the remaining 203 patients, who were still in the "gray zone" at 72 hours, a predictive model including unfavorable EEG patterns at 12 hours, absent or extensor motor response to pain at 72 hours, and higher age had an area under the curve of 0.90 (95% confidence interval 0.84-0.96). Favorable EEG patterns at 12 hours were strongly associated with good outcome. EEG beyond 24 hours had no additional predictive value.
Conclusions: EEG within 24 hours is a robust contributor to prediction of poor or good outcome of comatose patients after cardiac arrest.

Gepubliceerd: Neurology 2015 Jun 12;85(2):137-43
Impact factor: 8.185

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5. Diaphragm muscle fiber weakness and ubiquitin-proteasome activation in critically ill patients
Hooijman PE, Beishuizen A, Witt CC, de Waard MC, Girbes AR, Spoelstra-de Man AM, Niessen HW, Manders E, van Hees HW, van den Brom CE, Silderhuis V, Lawlor MW, Labeit S, Stienen GJ, Hartemink KJ, Paul MA, Heunks LM, Ottenheijm CA

Rationale: The clinical significance of diaphragm weakness in critically ill patients is evident: it prolongs ventilator dependency, and increases morbidity and duration of hospital stay. To date, the nature of diaphragm weakness and its underlying pathophysiologic mechanisms are poorly understood.

Objectives: We hypothesized that diaphragm muscle fibers of mechanically ventilated critically ill patients display atrophy and contractile weakness, and that the ubiquitin-proteasome pathway is activated in the diaphragm.
Methods: We obtained diaphragm muscle biopsies from 22 critically ill patients who received mechanical ventilation before surgery and compared these with biopsies obtained from patients during thoracic surgery for resection of a suspected early lung malignancy (control subjects). In a proof-of-concept study in a muscle-specific ring finger protein-1 (MuRF-1) knockout mouse model, we evaluated the role of the ubiquitin-proteasome pathway in the development of contractile weakness during mechanical ventilation.
Measurements and main results: Both slow- and fast-twitch diaphragm muscle fibers of critically ill patients had approximately 25% smaller cross-sectional area, and had contractile force reduced by half or more. Markers of the ubiquitin-proteasome pathway were significantly up-regulated in the diaphragm of critically ill patients. Finally, MuRF-1 knockout mice were protected against the development of diaphragm contractile weakness during mechanical ventilation.
Conclusions: These findings show that diaphragm muscle fibers of critically ill patients display atrophy and severe contractile weakness, and in the diaphragm of critically ill patients the ubiquitin-proteasome pathway is activated. This study provides rationale for the development of treatment strategies that target the contractility of diaphragm fibers to facilitate weaning.

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Impact factor: 12.996

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6. Successful treatment of fulminant postoperative bleeding due to acquired haemophilia
Mekenkamp LJ, Beishuizen A, Slomp J, Legdeur MC, Klaase JM, Trof RJ

Acquired haemophilia is a rare but life-threatening phenomenon in patients who have undergone surgical treatment. We describe a patient with a history of pancreatic cancer and a conventional pancreaticoduodenectomy, who underwent elective resection of an enterocutaneous fistula, complicated by fulminant haemorrhagic shock, caused by acquired haemophilia A. Eventually, the bleeding was controlled by a combination of aggressive haemostatic and immunosuppressive therapy. Prompt diagnosis of acquired haemophilia is crucial to allow early and appropriate haemostatic treatment and reduce the period of increased bleeding risk by eradicating the inhibitor with immunosuppressive therapy.

Gepubliceerd: Neth J Med 2015 May;73(4):182-6
Impact factor: 1.969

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7. Agranulocytosis and septic shock after metamizole use
Oude Munnink TH, Annink-Smoors M, Hom HW, Sportel ET

Background: Metamizole is an analgesic, the orally administered form of which was withdrawn in the Netherlands in 1989 due to an unacceptably high incidence of agranulocytosis. However, later studies showed a much lower incidence and since 2013 the use of metamizole has been recommended by the national guideline on postoperative pain.
Case description: A 58-year-old woman was referred by her general practitioner to our hospital with suspected diverticulitis. Three days previously the patient had returned from a four-week period of rehabilitation at a German spa following hip replacement surgery. She had been using metamizole since the operation. Within hours of admission, the patient developed septic shock and was transferred to the intensive care unit. Laboratory tests revealed severe neutropenia of 0.2 x 109/l. Treatment consisted of filgrastim, piperacillin/tazobactam and haemodynamic support. After five days the patient was sufficiently recovered to return to the ward.
Conclusion: Metamizole-related agranulocytosis is rare but potentially life-threatening. This condition is expected to occur more frequently as the use of metamizole in the Netherlands increases.

Gepubliceerd: Ned Tijdschr Geneeskd 2015;160:A9464
Impact factor: 0

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8. Ultrarapid Induction of Hypothermia Using Continuous Automated Peritoneal Lavage With Ice-Cold Fluids: Final Results of the Cooling for Cardiac Arrest or Acute ST-Elevation Myocardial Infarction Trial
Polderman KH, Noc M, Beishuizen A, Biermann H, Girbes AR, Tully GW, Seidman D, Albertsson PA, Holmberg M, Sterz F, Holzer M

Objectives: Hypothermia (32-34 degrees C) can mitigate ischemic brain injury, and some evidence suggests that it can reduce infarct size in acute myocardial infarction and acute ischemic stroke. For some indications, speed of cooling may be crucial in determining efficacy. We performed a multicenter prospective intervention study to test an ultrarapid cooling technology, the Velomedix Automated Peritoneal Lavage System using ice-cold fluids continuously circulating through the peritoneal cavity to rapidly induce and maintain hypothermia in comatose patients after cardiac arrest and a small number of awake patients with acute myocardial infarction.
Design: Multicenter prospective intervention study.
Setting: Intensive care- and coronary care units of multiple tertiary referral centers.
Measurements and main results: Access to the peritoneal cavity was gained using a modified blunt dilating instrument, followed by catheter placement. Patients were cooled to a temperature of 32.5 degrees C, maintained for 24 hours (cardiac arrest) or 3 hours (acute myocardial infarction) followed by controlled rewarming. Forty-nine patients were enrolled, and 46 patients completed treatment. One placement was unsuccessful (abdominal wall not breached), two patients were ultimately not cooled, and only safety data are reported. Average catheter insertion time was 2.3 minutes. Mean time to temperature less than 33 degrees C was 10.4 minutes (average cooling rate, 14 degrees C/hr). Median infarct size in patients who had coronary interventions was 16% of LV. No cases of stent thrombosis occurred. Survival in cardiac arrest patients with initial rhythm of ventricular

tachycardia/ventricular fibrillation was 56%, of whom 82 had a complete neurologic recovery. This compares favorably to outcomes from previous studies.
Conclusion: Automated peritoneal lavage system is a safe and ultrarapid method to induce and maintain hypothermia, which appears feasible in cardiac arrest patients and awake patients with acute myocardial infarction. The shivering response appeared to be delayed and much reduced with this technology, diminishing metabolic disorders associated with cooling and minimizing sedation requirement. Our data suggest that ultrarapid cooling could prevent subtle neurologic damage compared with slower cooling. This will need to be confirmed in direct comparative studies.

Gepubliceerd: Crit Care Med 2015 Jul 17;43(10):2191-201
Impact factor: 6.312

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9. Coagulation, Fibrinolysis and Inhibitors in Failing Filters during Continuous Venovenous Hemofiltration in Critically Ill Patients with Acute Kidney Injury: Effect of Anticoagulation Modalities
Schilder L, Nurmohamed SA, Ter Wee PM, Paauw NJ, Girbes AR, Beishuizen A, Beelen RH, Groeneveld AB

Introduction: The mechanisms of early filter failure and clotting with different anticoagulation modalities during continuous venovenous hemofiltration (CVVH) are largely unknown.
Methods: Citrate, heparin and no anticoagulation were compared. Blood was drawn pre- and post filter up to 720 min. Concentrations of the thrombin-antithrombin (TAT), activated protein C-protein C inhibitor (APC-PCI), and type I plasminogen activator inhibitor (PAI-1) were determined.
Results: In case of early filter failure (<24 h), inlet concentrations of TAT and APC-PCI were higher over time, irrespective of anticoagulation. There was more production of APC-PCI and platelet-derived PAI-1 in the filter after 10 min in the heparin group than in other groups. In clotting filters, production of APC-PCI and PAI was also higher with heparin than citrate.
Conclusion: Coagulation activation in plasma and inhibition of anticoagulation in plasma and filter may partly determine early CVVH filter failure due to clotting, particularly when heparin is used. Regional anticoagulation by citrate circumvents the inhibition of anticoagulation and fibrinolysis by platelet activation following heparin. (c) 2015 S. Karger AG, Basel.

Gepubliceerd: Blood Purif 2015;39(4):297-305
Impact factor: 1.284

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10. Putative novel mediators of acute kidney injury in critically ill patients: handling by continuous venovenous hemofiltration and effect of anticoagulation modalities
Schilder L, Nurmohamed SA, Ter Wee PM, Paauw NJ, Girbes AR, Beishuizen A, Beelen RH, Groeneveld AB

Background: Novel putative mediators of acute kidney injury (AKI) include immune-cell derived tumour necrosis factor-like weak inducer of apoptosis (TWEAK), angiopoietin-2 (Ang-2) and protein pentraxin-3 (PTX3). The effect of continuous venovenous hemofiltration (CVVH) and different anticoagulation regimens on plasma levels were studied.
Methods: At 0, 10, 60, 180 and 720 min of CVVH, samples were collected from pre- and postfilter blood and ultrafiltrate. No anticoagulation (n = 13), unfractionated heparin (n = 8) or trisodium citrate (n = 21) were compared.
Results: Concentrations of TWEAK, Ang-2 and PTX3 were hardly affected by CVVH since the mediators were not (TWEAK, PTX3) or hardly (Ang-2) detectable in ultrafiltrate, indicating negligible clearance by the filter in spite of molecular sizes (TWEAK, PTX3) at or below the cutoff of the membrane. Heparin use, however, was associated with an increase in in- and outlet plasma TWEAK.
Conclusion: Novel AKI mediators are not cleared nor produced by CVVH. However, heparin anticoagulation increased TWEAK levels in patient's plasma whereas citrate did not, favouring the latter as anticoagulant in CVVH for AKI.

Gepubliceerd: BMC Nephrol 2015;16(1):178
Impact factor: 1.690

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11. Gastric feeding intolerance is not caused by mucosal ischemia measured by intragastric air tonometry in the critically ill
Streefkerk JO, Beishuizen A, Groeneveld AB

Background: Gastric mucosal ischemia may be a risk factor for gastrointestinal intolerance to early feeding in the critically ill.
Aims: To study intragastric PCO2 air tonometry and gastric residual volumes (GRV) before and after the start of gastric feeding.
Methods: This is a two-center study in intensive care units of a university and teaching hospital. Twenty-nine critically ill, consecutive and consenting patients scheduled to start gastric feeding were studied after insertion of a gastric tonometry catheter and prior to and after start of gastric feeding (500 ml over 1 h), when clinically indicated.
Results: Blood gasometry and intragastric tonometry were performed prior to and 2 h after gastric feeding. The intragastric to arterial PCO2 gap (normal <8 mm Hg) was elevated in 41% of patients prior to feeding and measured (mean +/- standard deviation) 13 +/- 20 and 16 +/- 23 mm Hg in patients with normal (<100 ml, 42 +/- 34 ml, n = 19) and elevated GRV (250 +/- 141 ml, n = 10, P = 0.75), respectively. After feeding, the gradient did not increase and measured 27 +/- 25 and 23 +/- 34 mm Hg, respectively (P = 0.80).
Conclusion: Gastric mucosal ischemia is not a major risk factor for intolerance to early gastric feeding in the critically ill.

Gepubliceerd: Clin Nutr 2015 Jun 3;4.476
Impact factor: 4.476

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12. Electroencephalogram Predicts Outcome in Patients With Postanoxic Coma During Mild Therapeutic Hypothermia
Tjepkema-Cloostermans MC, Hofmeijer J, Trof RJ, Blans MJ, Beishuizen A, van Putten MJ

Objective: To assess the value of electroencephalogram for prediction of outcome of comatose patients after cardiac arrest treated with mild therapeutic hypothermia.
Design: Prospective cohort study.
Setting: Medical ICU.
Patients: One hundred forty-two patients with postanoxic encephalopathy after cardiac arrest, who were treated with mild therapeutic hypothermia.
Measurements and main results: Continuous electroencephalogram was recorded during the first 5 days of ICU admission. Visual classification of electroencephalogram patterns was performed in 5-minute epochs at 12 and 24 hours after cardiac arrest by two independent observers, blinded for patients' conditions and outcomes. Patterns were classified as isoelectric, low voltage, epileptiform, burst-suppression, diffusely slowed, or normal. Burst-suppression was subdivided into patterns with and without identical bursts. Primary outcome measure was the neurologic outcome based on each patient's best achieved Cerebral Performance Category score within 6 months after inclusion. 67 patients (47%) had favorable outcome (Cerebral Performance Category, 1-2). In patients with favorable outcome, electroencephalogram patterns improved within 24 hours after cardiac arrest, mostly toward diffusely slowed or normal. At 24 hours after cardiac arrest, the combined group of isoelectric, low voltage, and "burst-suppression with identical bursts" was associated with poor outcome with a sensitivity of 48% (95% CI, 35-61) and a specificity of 100% (95% CI, 94-100). At 12 hours, normal or diffusely slowed electroencephalogram patterns were associated with good outcome with a sensitivity of 56% (95% CI, 41-70) and a specificity of 96% (95% CI, 86-100).
Conclusions: Electroencephalogram allows reliable prediction of both good and poor neurologic outcome of patients with postanoxic encephalopathy treated with mild therapeutic hypothermia within 24 hours after cardiac arrest.

Gepubliceerd: Crit Care Med 2015 Sep 23;43(1):159-67
Impact factor: 6.312

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13. Effects of Cell-Saving Devices and Filters on Transfusion in Cardiac Surgery: A Multicenter Randomized Study
Vermeijden WJ, van Klarenbosch J, Gu YJ, Mariani MA, Buhre WF, Scheeren TW, Hagenaars JA, Tan ME, Haenen JS, Bras L, van Oeveren W, van den Heuvel ER, de Vries AJ

Background: Cell-saving devices (CS) are frequently used in cardiac surgery to reduce transfusion requirements, but convincing evidence from randomized clinical trials is missing. Filtration of salvaged blood in combination with the CS is widely used to improve the quality of retransfused blood, but there are no data to justify this approach.

Methods: To determine the contribution of CS and filters on transfusion requirements, we performed a multicenter factorial randomized clinical trial in two academic and four nonacademic hospitals. Patients undergoing elective coronary, valve, or combined surgical procedures were included. The primary end point was the number of allogeneic blood products transfused in each group during hospital admission.
Results: From 738 included patients, 716 patients completed the study (CS+filter, 175; CS, 189; filter, 175; neither CS nor filter, 177). There was no significant effect of CS or filter on the total number of blood products (fraction [95% confidence interval]: CS, 0.96 [0.79, 1.18]; filter, 1.17 [0.96, 1.43]). Use of a CS significantly reduced red blood cell transfusions within 24 hours (0.75 [0.61,0.92]), but not during hospital stay (0.86 [0.71, 1.05]). Use of a CS was significantly associated with increased transfusions of fresh frozen plasma (1.39 [1.04, 1.86]), but not with platelets (1.25 [0.93, 1.68]). Use of a CS significantly reduced the percentage of patients who received any transfusion (odds ratio [95% confidence interval]: 0.67 [0.49, 0.91]), whereas filters did not (0.92 [0.68, 1.25]).
Conclusions: Use of a CS, with or without a filter, does not reduce the total number of allogeneic blood products, but reduces the percentage of patients who need blood products during cardiac surgery.

Gepubliceerd: Ann Thorac Surg 2015;99(1):26-32
Impact factor: 3.849

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14. Reply: To PMID 25440265
Vermeijden WJ, de Vries AJ

Gepubliceerd: Ann Thorac Surg 2015 Jul;100(1):378
Impact factor: 3.849

Totale impact factor: 66.644
Gemiddelde impact factor: 4.760

Aantal artikelen 1e, 2e of laatste auteur: 5
Totale impact factor: 27.139
Gemiddelde impact factor: 5.428

Interne Geneeskunde

1. Neo-adjuvant chemotherapy followed by surgery versus surgery alone in high-risk patients with resectable colorectal liver metastases: the CHARISMA randomized multicenter clinical trial
Ayez N, van der Stok EP, de Wilt H, Radema SA, van Hillegersberg R, Roumen RM, Vreugdenhil G, Tanis PJ, Punt CJ, De Jong CA, Jansen RL, Verheul HM, de Jong KP, Hospers GA, Klaase JM, Legdeur MC, van Meerten E, Eskens FA, van der Meer N, van der Holt B, Verhoef C, Grunhagen DJ

Background: Efforts to improve the outcome of liver surgery by combining curative resection with chemotherapy have failed to demonstrate definite overall survival benefit. This may partly be due to the fact that these studies often involve strict inclusion criteria. Consequently, patients with a high risk profile as characterized by Fong's Clinical Risk Score (CRS) are often underrepresented in these studies. Conceptually, this group of patients might benefit the most from chemotherapy. The present study evaluates the impact of neo-adjuvant chemotherapy in high-risk patients with primary resectable colorectal liver metastases, without extrahepatic disease. Our hypothesis is that adding neo-adjuvant chemotherapy to surgery will provide an improvement in overall survival (OS) in patients with a high-risk profile.
Mehtods/Design: CHARISMA is a multicenter, randomized, phase III clinical trial. Patients will be randomized to either surgery alone (standard treatment, arm A) or to 6 cycles of neo-adjuvant oxaliplatin-based chemotherapy, followed by surgery (arm B). Patients must be >/= 18 years of age with liver metastases of histologically confirmed primary colorectal carcinoma. Patients with extrahepatic metastases are excluded. Liver metastases must be deemed primarily resectable. Only patients with a CRS of 3-5 are eligible. The primary study endpoint is OS. Secondary endpoints are progression free survival (PFS), quality of life, morbidity of resection, treatment response on neo-adjuvant chemotherapy, and whether CEA levels can predict treatment response.
Discussion: CHARISMA is a multicenter, randomized, phase III clinical trial that will provide an answer to the question if adding neo-adjuvant chemotherapy to surgery will improve OS in a well-defined high-risk patient group with colorectal liver metastases.
Trial registration: The CHARISMA is registered at European Union Clinical Trials Register (EudraCT), number: 2013-004952-39 and in the "Netherlands national Trial Register (NTR), number: 4893.

Gepubliceerd: BMC Cancer 2015;15:180
Impact factor: 3.362

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2. Comparative therapeutic value of post remission approaches in patients with acute myeloid leukemia aged 40-60 years
Cornelissen JJ, Versluis J, Passweg JR, van Putten WL, Manz MG, Maertens J, Beverloo HB, Valk PJ, van Marwijk KM, Wijermans PW, Schaafsma MR, Biemond BJ, Vekemans MC, Breems DA, Verdonck LF, Fey MF, Jongen-Lavrencic M,

Janssen JJ, Huls G, Kuball J, Pabst T, Graux C, Schouten HC, Gratwohl A, Vellenga E, Ossenkoppele G, Lowenberg B

The preferred type of post-remission therapy (PRT) in patients with acute myeloid leukemia (AML) in first complete remission (CR1) is a subject of continued debate, especially in patients at higher risk of non-relapse mortality (NRM), including patients >40 years of age. We report results of a time-dependent multivariable analysis of alloHSCT (n=337) versus chemotherapy (n=271) or autologous HSCT (n=152) in 760 patients aged 40 and 60 years with AML in CR1. Patients receiving alloHSCT showed improved survival (OS) as compared to chemotherapy (respectively 57+/-3% vs 40+/-3% at 5 years, P<0.001). Comparable OS was observed following alloHSCT and autoHSCT in patients with intermediate risk AML (60+/-4% vs 54+/-5%). However, alloHSCT was associated with less relapse (HR 0.51, P<0.001) and better RFS (HR 0.74, P=0.029) as compared to autoHSCT in intermediate risk AMLs. AlloHSCT was applied following myeloablative conditioning (n=157) or reduced intensity conditioning (n=180), resulting in less NRM, but comparable outcome with respect to OS, RFS, and relapse. Collectively, these results show that alloHSCT is to be preferred over chemotherapy as PRT in patients with intermediate and poor risk AML aged 40-60 years, while autoHSCT remains a treatment option to be considered in patients with intermediate risk AML.

Gepubliceerd: Leukemia 2015;29(5):1041-50
Impact factor: 10.431

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3. Th17 cytokine deficiency in patients with Aspergillus skull base osteomyelitis

Delsing CE, Becker KL, Simon A, Kullberg BJ, Bleeker-Rovers CP, van de Veerdonk FL, Netea MG

Background: Fungal skull base osteomyelitis (SBO) is a severe complication of otitis externa or sinonasal infection, and is mainly caused by Aspergillus species. Here we investigate innate and adaptive immune responses in patients with Aspergillus SBO to identify defects in the immune response that could explain the susceptibility to this devastating disease.
Methods: Peripheral blood mononuclear cells isolated from six patients with Aspergillus SBO and healthy volunteers were stimulated with various microbial stimuli, among which also the fungal pathogens Candida albicans and Aspergillus fumigatus. The proinflammatory cytokines IL-6, TNFalpha and IL-1beta, and the T-helper cell-derived cytokines IFNgamma, IL-17 and IL-22 were measured in cell culture supernatants by ELISA.
Results: Proinflammatory cytokine responses did not differ between SBO patients and healthy volunteers. The Candida- and Aspergillus-specific Th17 response (production of IL-17 and IL-22) was significantly decreased in the SBO patients compared to healthy individuals, while Th1 cytokine response (IFNgamma production) did not differ between the two groups.
Conclusions: We show that patients with Aspergillus skull base osteomyelitis infection have specific defects in Th17 responses. Since IL-17 and IL-22 are

important for stimulating antifungal host defense, we hypothesize that strategies that have the ability to improve IL-17 and IL-22 production may be useful as adjuvant immunotherapy in patients with Aspergillus SBO.

Gepubliceerd: BMC Infect Dis 2015;15:140
Impact factor: 2.613

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4. Quality of life of patients with chronic lymphocytic leukaemia in the Netherlands: results of a longitudinal multicentre study
Holtzer-Goor KM, Schaafsma MR, Joosten P, Posthuma EF, Wittebol S, Huijgens PC, Mattijssen EJ, Vreugdenhil G, Visser H, Peters WG, Erjavec Z, Wijermans PW, Daenen SM, van der Hem KG, van Oers MH, Uyl-de Groot CA

Purpose: To describe the health-related quality of life (HRQoL) of an unselected population of patients with chronic lymphocytic leukaemia (CLL) including untreated patients.
Methods: HRQoL was measured by the EORTC QLQ-C30 including the CLL16 module, EQ-5D, and VAS in an observational study over multiple years. All HRQoL measurements per patient were connected and analysed using area under the curve analysis over the entire study duration. The total patient group was compared with the general population, and three groups of CLL patients were described separately, i.e. patients without any active treatment ("watch and wait"), chlorambucil treatment only, and patients with other treatment(s).
Results: HRQoL in the total group of CLL patients was compromised when compared with age- and gender-matched norm scores of the general population. CLL patients scored statistically worse on the VAS and utility score of the EQ-5D, all functioning scales of the EORTC QLQ-C30, and the symptoms of fatigue, dyspnoea, sleeping disturbance, appetite loss, and financial difficulties. In untreated patients, the HRQoL was slightly reduced. In all treatment stages, HRQoL was compromised considerably. Patients treated with chlorambucil only scored worse on the EORTC QLQ-C30 than patients who were treated with other treatments with regard to emotional functioning, cognitive functioning, bruises, uncomfortable stomach, and apathy.
Conclusions: CLL patients differ most from the general population on role functioning, fatigue, concerns about future health, and having not enough energy. Once treatment is indicated, HRQoL becomes considerably compromised. This applies to all treatments, including chlorambucil, which is considered to be a mild treatment.

Gepubliceerd: Qual Life Res 2015 Jul 24;24(12):2895-906
Impact factor: 2.486

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5. Differentiation of Acute Q Fever from Other Infections in Patients Presenting to Hospitals, the Netherlands
Keijmel SP, Krijger E, Delsing CE, Sprong T, Nabuurs-Franssen MH, Bleeker-Rovers CP

Differentiating acute Q fever from infections caused by other pathogens is essential. We conducted a retrospective case-control study to evaluate differences in clinical signs, symptoms, and outcomes for 82 patients with acute Q fever and 52 control patients who had pneumonia, fever and lower respiratory tract symptoms, or fever and hepatitis, but had negative serologic results for Q fever. Patients with acute Q fever were younger and had higher C-reactive protein levels but lower leukocyte counts. However, a large overlap was found. In patients with an indication for prophylaxis, chronic Q fever did not develop after patients received prophylaxis but did develop in 50% of patients who did not receive prophylaxis. Differentiating acute Q fever from other respiratory infections, fever, or hepatitis is not possible without serologic testing or PCR. If risk factors for chronic Q fever are present, prophylactic treatment is advised.

Gepubliceerd: Emerg Infect Dis 2015 Aug;21(8):1348-56
Impact factor: 6.751

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6. Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial
Kordes S, Pollak MN, Zwinderman AH, Mathot RA, Weterman MJ, Beeker A, Punt CJ, Richel DJ, Wilmink JW

Background: In preclinical work and retrospective population studies, the anti-diabetic drug metformin has been associated with antineoplastic activity and decreased burden of many cancers, including pancreatic cancer. There is therefore interest in the hypothesis that this drug might be repurposed for indications in oncology. We aimed to assess the efficacy of the addition of metformin to a standard systemic therapy in patients with advanced pancreatic cancer, and provide the first report of a clinical trial with a survival endpoint of metformin for an oncological indication.
Methods: We did this double-blind, randomised, placebo-controlled phase 2 trial at four centres in the Netherlands. Patients aged 18 years or older with advanced pancreatic cancer were randomly assigned (1:1), via a permutated computer-generated block allocation scheme (block size of six) to receive intravenous gemcitabine (1000 mg/m(2)) on days 1, 8, and 15 every 4 weeks and oral erlotinib (100mg) once daily in combination with either oral metformin or placebo twice daily. Metformin dose was escalated from 500 mg (in the first week) to 1000 mg twice daily in the second week. Randomisation was stratified by hospital, diabetes status, and tumour stage. The primary endpoint was overall survival at 6 months in the intention-to-treat population. This trial is complete and is registered with ClinicalTrials.gov, number NCT01210911.
Findings: Between May 31, 2010, and Jan 3, 2014, we randomly assigned 121 patients to receive gemcitabine and erlotinib with either placebo (n=61) or metformin (n=60). Overall survival at 6 months was 63.9% (95% CI 51.9-75.9) in the placebo group and 56.7% (44.1-69.2) in the metformin group (p=0.41). There was no difference in overall survival between groups (median 7.6 months [95% CI 6.1-9.1] vs 6.8 months [95% CI 5.1-8.5] in the metformin group; hazard ratio [HR] 1.056

[95% CI 0.72-1.55]; log-rank p=0.78). The most frequent grade 3-4 toxic effects were neutropenia (15 [25%] patients in placebo group vs 15 [25%] in metformin group), skin rash (six [10%] vs four [7%]), diarrhoea (three [5%] vs six [10%]), and fatigue (two [3%] vs six [10%]).
Interpretation: Addition of a conventional anti-diabetic dose of metformin does not improve outcome in patients with advanced pancreatic cancer treated with gemcitabine and erlotinib. Future research should include studies of more potent biguanides, and should focus on patients with hyperinsulinaemia and patients with tumours showing markers of sensitivity to energetic stress, such as loss of function of AMP kinase, a key regulator of cellular energy homoeostasis.
Funding: Academic Medical Centre, Amsterdam and The Terry Fox Foundation, Vancouver, Canada.

Gepubliceerd: Lancet Oncol 2015 Jul;16(7):839-47
Impact factor: 24.690

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7. Phase II study of capecitabine and the oral mTOR inhibitor everolimus in patients with advanced pancreatic cancer
Kordes S, Klumpen HJ, Weterman MJ, Schellens JH, Richel DJ, Wilmink JW

Purpose: The combination of an mTOR inhibitor with 5-fluorouracil-based anticancer therapy is attractive because of preclinical evidence of synergy between these drugs. According to our phase I study, the combination of capecitabine and everolimus is safe and feasible, with potential activity in pancreatic cancer patients.
Methods: Patients with advanced adenocarcinoma of the pancreas were enrolled. Eligible patients had a WHO performance status 0-2 and adequate hepatic and renal functions. The treatment regimen consisted of capecitabine 1000 mg/m(2) BID day 1-14 and everolimus 10 mg daily (5 mg BID) in a continuous 21-day schedule. Tumor assessment was performed with CT-scan every three cycles. Primary endpoint was response rate (RR) according to RECIST 1.0. Secondary endpoints were progression-free survival, overall survival and 1-year survival rate.
Results: In total, 31 patients were enrolled. Median (range) treatment duration with everolimus was 76 days (1-431). Principal grade 3/4 toxicities were hyperglycemia (45 %), hand-foot syndrome (16 %), diarrhea (6 %) and mucositis (3 %). Prominent grade 1/2 toxicities were anemia (81 %), rash (65 %), mucositis (58 %) and fatigue (55 %). RR was 6 %. Ten patients (32 %) had stable disease resulting in a disease control rate of 38 %. Median overall survival was 8.9 months (95 % CI 4.6-13.1). Progression-free survival was 3.6 months (95 % CI 1.9-5.3).
Conclusions: The oral regimen with the combination of capecitabine and everolimus is a moderately active treatment for patients with advanced pancreatic cancer, with an acceptable toxicity profile at the applied dose level.

Gepubliceerd: Cancer Chemother Pharmacol 2015 Jun;75(6):1135-41
Impact factor: 2.769

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8. How did partners experience cancer patients' participation in a phase I study? An observational study after a patient's death
Langenberg SM, Peters ME, van der Graaf WT, Wymenga AN, Prins JB, van Herpen CM

Objective: It can be assumed that patients' participation in a phase I study will have an important impact on their partners' life. However, evaluation of partners' experiences while patients are undergoing experimental treatment and of their well-being after the patient's death is lacking. We aimed to explore partners' experience of patients' participation in phase I studies and to investigate their well-being after a patient's death.
Method: This was an observational study conducted after the patient's death. Partners of deceased patients who had participated in a phase I study completed a questionnaire designed by us for experience evaluation and the Beck Depression Inventory for Primary Care, the Hospital Anxiety and Depression Scale, the Inventory of Traumatic Grief, and the RAND-36 Health Survey.
Results: The median age of the 58 participating partners was 58 years (range: 51-65), and 67% was female. Partners reported negative effects on patients' quality of life, but only 5% of partners regretted patients' participation. Approximately two years after the patients' death, 19% of partners scored for depression, 36% for psychological distress, and 46% for complicated grief, and partners generally scored significantly lower on social and mental functioning compared to normative comparators.
Significance of results: Although partners reported negative consequences on patients' quality of life, most did not regret patients' participation in the phase I studies. Prevalence of depression, psychological distress, and complicated grief seemed important problems after a patient's death, and these must be considered when shaping further support for partners of patients participating in phase I trials.

Gepubliceerd: Palliat Support Care 2015 Dec 17;1-9
Impact factor: 0

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9. Successful treatment of fulminant postoperative bleeding due to acquired haemophilia
Mekenkamp LJ, Beishuizen A, Slomp J, Legdeur MC, Klaase JM, Trof RJ

Acquired haemophilia is a rare but life-threatening phenomenon in patients who have undergone surgical treatment. We describe a patient with a history of pancreatic cancer and a conventional pancreaticoduodenectomy, who underwent elective resection of an enterocutaneous fistula, complicated by fulminant haemorrhagic shock, caused by acquired haemophilia A. Eventually, the bleeding was controlled by a combination of aggressive haemostatic and immunosuppressive therapy. Prompt diagnosis of acquired haemophilia is crucial to allow early and appropriate haemostatic treatment and reduce the period of increased bleeding risk by eradicating the inhibitor with immunosuppressive therapy.

Gepubliceerd: Neth J Med 2015 May;73(4):182-6

Impact factor: 1.969

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10. The standardised mortality ratio: the proper quality indicator in acute leukaemia?
Saes L, Peters WG, Schaafsma R, van Spronsen DJ, van der Velden AW, van den Bosch WF, Meijer E

Background: The standardised mortality ratio (SMR) is a quality indicator used to measure quality of care in the Netherlands. It is subject to much criticism, which was the reason to study the value of the SMR as a quality indicator for the treatment of acute leukaemia.
Methods: A retrospective analysis was performed in patients with acute leukaemia admitted to a Santeon hospital during the period 2005-2009. SMR values were calculated and compared with the overall survival (OS).
Results: During the study period, 455 unique patients were admitted with acute leukaemia. SMR calculation was based on 992 admissions. SMR analysis yielded a high mortality ratio in hospital 1, 2, 3 and 4 in comparison with the national average (100), significant for hospital 1 and 4 (180 [CI 95% 126-257] and 187 [CI 95% 134-261], respectively) OS analysis also showed a significantly different outcome between hospitals. However, using OS as outcome parameter, hospital 2 and 6 showed the lowest performance as compared with hospital 1 and 4 using SMR as parameter. After multivariate analysis, age (HR 1.04; CI 95% 1.03-1.05; $p < 0.001$) and hospital (hospital 5 compared with 6: HR 0.54; CI 95% 0.30- .98; $p = 0.043$; hospital 2 compared with 1: HR 1.51; CI 95% 1.02-2.23; $p = 0.039$) were the only significant variables that influenced OS.
Conclusion: Outcome according to SMR is not equivalent to outcome according to OS. This study shows that the use of the SMR as a quality indicator for the treatment of acute leukaemia does not appear to be justified.

Gepubliceerd: Neth J Med 2015 Mar;73(3):119-23
Impact factor: 1.969

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11. Circulating tumor cells before and during follow-up after breast cancer surgery
van Dalum G, van der Stam GJ, Tibbe AG, Franken B, Mastboom WJ, Vermes I, de Groot MR, Terstappen LW

The presence of circulating tumor cells (CTC) is an independent prognostic factor for progression-free and overall survival for patients with metastatic and newly diagnosed breast cancer. The present study was undertaken to explore whether the presence of CTC before and during follow-up after surgery is associated with recurrence free survival (RFS) and overall survival (OS). In a prospective single center study, CTC were enumerated with the CellSearch system in 30 ml of peripheral blood of 403 stage I-III patients before undergoing surgery for breast cancer (A) and if available 1 week after surgery (B), after adjuvant chemo- and/or radiotherapy or before start of long-term hormonal therapy (C), one (D), two (E) and

three (F) years after surgery. Patients were stratified into unfavorable (CTC >/=1) and favorable (CTC=0) prognostic groups. >1 CTC in 30 ml blood was detected in 75/403 (19%) at A, 66/367 (18%) at B, 40/263 (15%) at C, 30/235 (12%) at D, 18/144 (11%) at E and 11/83 (13%) at F. RFS and OS was significantly lower for unfavorable CTC as compared to favorable CTC before surgery (p=0.022 and p=0.006), after adjuvant therapy (p<0.001 and p=0.018) and one (p=0.006 and p=0.013) and two (p<0.001 and p=0.045) years after surgery, but not 1 week post-surgery. The presence of CTC in blood drawn pre and one and two years after surgery, but not post-surgery is associated with shorter RFS and OS for stage I-III breast cancer.

Gepubliceerd: Int J Oncol 2015 Oct 6;46(1):407-13
Impact factor: 3.025

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12. Importance of circulating tumor cells in newly diagnosed colorectal cancer
van Dalum G, Stam GJ, Scholten LF, Mastboom WJ, Vermes I, Tibbe AG, de Groot MR, Terstappen LW

Presence of circulating tumor cells (CTC) is associated with poor prognosis in patients with metastatic colorectal cancer (CRC). The present study was conducted to determine if the presence of CTC prior to surgery and during followup in patients with newly diagnosed non-metastatic CRC can identify patients at risk for disease recurrence. In a prospective single center study 183 patients with newly diagnosed non-disseminated CRC, scheduled for surgery, were enrolled and followed-up for a median of 5.1 years. CTC were enumerated with the CellSearch system in 4 aliquots of 7.5 ml of blood before surgery and at several time-points during follow-up after surgery. The results showed that >/=1 CTC/30 ml of blood were detected in 44 (24%) patients before surgery. Patients with CTC before surgery had a significant decrease in recurrence-free survival (RFS, log-rank test p=0.014) and colon cancer related survival (CCRS, p=0.002). The 5-year RFS dropped from 75 to 61% and the 5-year CCRS from 83 to 69% for patients with CTC before surgery. The presence of CTC and positive lymph nodes remained significant factors in multivariate analysis for recurrence-free survival (RFS). Surprisingly, the presence of CTC weeks after surgery was not significantly associated with RFS and CCRD whereas CTC 2-3 years after surgery was again significantly associated with RFS and CCRD. The presence of CTC in patients with stage I-III CRC before surgery is associated with a significant reduction in RFS and CCRS. These findings suggest a role of CTC detection to assess which patients need adjuvant treatment.

Gepubliceerd: Int J Oncol 2015 Mar;46(3):1361-8
Impact factor: 3.025

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13. Synthetic ACTH in High Risk Patients with Idiopathic Membranous Nephropathy: A Prospective, Open Label Cohort Study
van de Logt AE, Beerenhout CH, Brink HS, van de Kerkhof JJ, Wetzels JF, Hofstra JM

Trial registration: ClinicalTrials.gov NCT00694863.

Gepubliceerd: PLoS One 2015;10(11):e0142033
Impact factor: 3.234

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14. Phase I and pharmacological trial of lapatinib in combination with gemcitabine in patients with advanced breast cancer
van der Noll R, Smit WM, Wymenga AN, Boss DS, Grob M, Huitema AD, Rosing H, Tibben MM, Keessen M, Rehorst H, Beijnen JH, Schellens JH

Background: Lapatinib has proven efficacy as monotherapy and in combination with capecitabine in patients with metastatic breast cancer (MBC) overexpressing HER2 and/or EGFR. Gemcitabine also has anti-tumor activity in MBC and a favourable toxicity profile. In this phase I study lapatinib and gemcitabine were combined.
Methods: Female patients with advanced BC were given lapatinib once daily (QD) in 28-day cycles with gemcitabine administered on day 1, 8 and 15. Physical examinations, vital signs and blood sampling for hematology, clinical chemistry and pharmacokinetics (PK) and radiological assessments of disease were performed at regular intervals.
Results: In total, 33 patients were included. Six dose-limiting toxicities were observed, mostly grade 3 increases in liver function tests. Most common toxicities were fatigue (73 %), nausea (70 %), diarrhea (58 %), increases in ALAT and ASAT (55 and 52 %, respectively) and rash (46 %). The maximum tolerated dose was lapatinib 1250 mg QD with gemcitabine 1000 mg/m(2). Lapatinib and gemcitabine PK did not appear to be influenced by each other. Anti-tumor activity was observed with one patient (4 %) showing complete response and six (23 %) partial response.
Conclusion: Despite a slightly increased toxicity profile compared to their respective monotherapies, lapatinib and gemcitabine can be safely combined while showing signs of anti-tumor activity.

Gepubliceerd: Invest New Drugs 2015 Dec;33(6):1197-205
Impact factor: 2.919

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15. Bevacizumab in combination with radiotherapy and temozolomide for patients with newly diagnosed glioblastoma multiforme
van Linde ME, Verhoeff JJ, Richel DJ, van Furth WR, Reijneveld JC, Verheul HM, Stalpers LJ

Background: Patients with a newly diagnosed glioblastoma multiforme (GBM) have a high risk of recurrent disease with a dismal outcome despite intensive treatment of sequential surgery and chemoradiotherapy with temozolomide (TMZ), followed by TMZ as a single agent. Bevacizumab (BV) may increase response rates to chemotherapy in the recurrent treatment setting of GBM. We hypothesized that a neoadjuvant treatment strategy for patients with newly diagnosed GBM using

chemoradiotherapy plus BV would improve resectability and thus survival. We performed a phase II trial of the treatment strategy of BV plus chemoradiation to determine the safety of this combination in patients who had already undergone primary surgery for their GBM.
Methods: After a biopsy (6 patients) or a resection (13 patients) of a newly diagnosed GBM, 19 patients received radiotherapy (30 fractions of 2 Gy) in combination with daily TMZ 75 mg/m(2) and BV 10 mg/kg on days 1, 14, and 28, followed by 6 monthly cycles of TMZ 150-200 mg/m(2) on days 1-5.
Results: The overall response rate was 26%. Three patients had a complete response after resection, and in two patients, a complete response after resection followed by chemoradiation plus BV was seen. No grade 3-4 toxicities were observed during combination treatment. The median progression-free survival was 9.6 months (95% confidence interval [CI]: 4.3-14.4 months). The median overall survival was 16 months (95% CI: 8.1-26.3 months), similar to a matched control group that received standard chemoradiotherapy from our institution.
Conclusion: Combination of bevacizumab with radiotherapy and TMZ is safe and feasible in patients with newly diagnosed GBM, but because of low response rates, this treatment strategy does not favor a neoadjuvant approach.

Gepubliceerd: Oncologist 2015 Feb;20(2):107-8
Impact factor: 4.865

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16. Multi-center randomized open label phase II trial on 3 rituximab dosing schemes in immune thrombocytopenia patients
Zwaginga JJ, van der Holt B, Te Boekhorst PA, Biemond BJ, Levin MD, van der Griend R, Brand A, Zweegman S, Pruijt HF, Novotny VM, Vreugdenhil A, de Groot MR, de Weerdt O, van Pampus EC, van Maanen-Lamme TM, Wittebol S, Schipperus MR, Silbermann MH, Huijgens PC, Luten M, Hollestein R, Brakenhoff JA, Schrama JG, Valster FA, Velders GA, Koene HR.

Gepubliceerd: Haematologica 2015;100(3):e90-e92
Impact factor: 5.814

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17. Phase 1a/1b and pharmacogenetic study of docetaxel, oxaliplatin and capecitabine in patients with advanced cancer of the stomach or the gastroesophageal junction
Deenen MJ, Meulendijks D, Boot H, Legdeur MC, Beijnen JH, Schellens JH, Cats A

Purpose: The prognosis of gastroesophageal cancer is poor, and current regimens are associated with limited efficacy. The purpose of this study was to explore the safety and preliminary efficacy of docetaxel, oxaliplatin plus capecitabine for advanced cancer of the stomach or the gastroesophageal junction (GEJ). Secondary objectives included pharmacokinetic and pharmacogenetic analyses.
Methods: Patients were treated in escalating dose levels with docetaxel and oxaliplatin (both on day 1), plus capecitabine b.i.d. on days 1-14 every 3 weeks, to determine the dose-limiting toxicity and maximum tolerated dose (MTD). An

expansion cohort was treated at the MTD. A total of ten polymorphisms in pharmacokinetic and pharmacodynamic candidate genes were analyzed and tested for association with treatment outcome.
Results: A total of 34 evaluable patients were enrolled. The MTD was docetaxel 50 mg/m(2), oxaliplatin 100 mg/m(2) plus capecitabine 850 mg/m(2) b.i.d. The median number of treatment cycles was 6 (range 2-8). Grade >/= 3 toxicities included neutropenia (24 %), leukocytopenia (15 %), febrile neutropenia (12 %), fatigue (9 %) and diarrhea (6 %). The overall response rate was 45 %; two patients achieved a complete response. Median progression-free survival and overall survival were 6.5 months (95 % CI 5.4-7.6) and 11.0 months (95 % CI 7.9-14.1), respectively. The polymorphisms ERCC1 354C>T, TYMS 1053C>T and rs2612091 in ENOSF1 were associated with severe toxicity; ERCC1 354C>T and ERCC2 2251A>C were associated with poor progression-free survival.
Conclusion: Docetaxel, oxaliplatin plus capecitabine are a well-tolerable, safe and effective treatment regimen for patients with advanced cancer of the stomach or GEJ. Pharmacogenetic markers in pharmacokinetic and pharmacodynamic candidate genes may be predictive for treatment outcome.

Cancer Chemother Pharmacol 2015 Dec;76(6):1285-95
Impact factor: 2.769

Totale impact factor: 91.715
Gemiddelde impact factor: 5.395

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 9.987
Gemiddelde impact factor: 2.497

Kindergeneeskunde

1. Adalimumab therapy in children with Crohn disease previously treated with infliximab
Cozijnsen M, Duif V, Kokke F, Kindermann A, van Rheenen P, de Meij T, Schaart M, Damen G, Norbruis O, Pelleboer R, Van den Neucker A, van Wering H, Hummel T, Oudshoorn J, Escher J, de Ridder L

Objectives: Adalimumab, a humanised anti-tumour necrosis factor antibody, is an effective treatment in adult patients with refractory Crohn disease (CD). The available literature on its efficacy in children remains limited. We aimed to evaluate the real-world efficacy in paediatric patients with CD and compare the efficacy between infliximab (IFX) nonresponders and patients who lost response to IFX.
Methods: All Dutch patients with CD receiving adalimumab before the age of 18 years after previous IFX therapy were identified. We analysed longitudinal disease activity, assessed by the mathematically weighted Pediatric Crohn's Disease Activity Index (wPCDAI) or the physician global assessment (PGA), and adverse events (AEs).
Results: Fifty-three patients with CD were included. Twelve patients received monotherapy and the others received combination treatment with thiopurines (n = 21), methotrexate (n = 11), steroids (n = 7), or exclusive enteral nutrition (n = 2). Median follow-up was 12 months (interquartile range 5-23). Remission was reached in 34 patients (64%, wPCDAI < 12.5 or PGA = 0) after a median of 3.3 months, and maintained by 50% for 2 years. Eleven patients (21%) reached response but not remission (decrease in wPCDAI >/= 17.5 or decrease in PGA). Eighteen patients (34%) failed adalimumab treatment because of nonresponse (n = 4), lost response (n = 11), or AEs (n = 3). More IFX nonresponders failed adalimumab treatment than patients who lost response to IFX (2/3 vs 8/34, hazard ratio 18.8, 95% confidence interval 1.1-303.6). Only 1 patient encountered a serious AE, a severe but nonfatal infection.
Conclusions: In clinical practice, adalimumab induces remission in two-thirds of children with IFX refractory CD.

Gepubliceerd: J Pediatr Gastroenterol Nutr 2015 Feb;60(2):205-10
Impact factor: 2.625

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2. Methotrexate for maintaining remission in paediatric Crohn's patients with prior failure or intolerance to thiopurines: a multicenter cohort study
Haisma SM, Lijftogt T, Kindermann A, Damen G, de Ridder L, Escher JC, Mearin ML, de Meij T, Hendriks D, Jorge E, Hummel T, Norbruis O, van Rheenen P

Background and Aims: Methotrexate [MTX] is an immunomodulating drug that can be used to maintain remission in patients with Crohn's disease [CD], but data on efficacy and tolerability in children and teenagers are scarce. We evaluated the long-term efficacy and tolerability of MTX monotherapy after thiopurine therapy in paediatric CD patients.

Methods: A multicenter cohort of paediatric MTX users who stopped thiopurines due to ineffectiveness or intolerance between 2002 and 2012 were included and followed for at least 12 months. Relapse-free use was defined as steroid and biologics-free clinical remission after the introduction of MTX, and included intentional discontinuation of successful therapy before the end of the observation period.
Results: A total of 113 patients with CD in remission were followed while on MTX monotherapy, of whom 75 [66%] had failed on thiopurines and 38 [34%] had stopped thiopurines due to side effects. Median age at the introduction of MTX was 14 years [range 7 to 17], and 93% used the subcutaneous route. Kaplan-Meier analysis showed that 52% of the study cohort were still in steroid- and biologics-free remission after 12 months of MTX monotherapy, with a difference that did not reach significance between thiopurine-intolerant and thiopurine-failing patients [p = 0.21, log-rank test].
Conclusions: The findings of this cohort study suggest that MTX is an effective immunomodulator to maintain remission after stopping thiopurines. MTX maintenance should be considered before stepping up to anti-tumor necrosis factor alpha therapy. MTX is probably somewhat more effective in patients who stopped thiopurines due to side effects than in those who failed on thiopurines.

Gepubliceerd: J Crohns Colitis 2015 Apr;9(4):305-11
Impact factor: 6.234

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3. The association of infliximab trough levels with disease activity in pediatric inflammatory bowel disease
Hoekman DR, Brandse JF, de Meij TG, Hummel TZ, Lowenberg M, Benninga MA, D'Haens GR, Kindermann A

Objective: Low serum trough levels (TLs) of infliximab (IFX) and antibodies to IFX (ATIs) are associated with the loss of therapeutic response in adults with inflammatory bowel disease (IBD) receiving IFX. Until now, pediatric data are scarce. Therefore, we aimed to cross-sectionally investigate the association between ATIs and IFX TLs, and clinical and biochemical disease activity in children receiving IFX for IBD.
Material and Methods: Children aged <18 years receiving IFX maintenance treatment for Crohn's disease (CD) or ulcerative colitis (UC) at three Dutch hospitals were included. Prior to two consecutive IFX infusions, IFX TLs and ATI levels were measured. Clinical disease activity was determined by Pediatric Crohn's Disease Activity Index (PCDAI) and Pediatric Ulcerative Colitis Activity Index (PUCAI), for CD and UC, respectively. Biochemical disease activity was assessed by serum C-reactive protein (CRP) and fecal calprotectin (FC). Clinical remission was defined as a PUCAI or PCDAI score of <10. Therapeutic range of IFX was considered 3-7 microg/ml.
Results: Thirty-nine patients were included (31 CD; 16 females). Median age was 15 years. Median IFX TL was 3.5 microg/ml [IQR 2-7]. Subtherapeutic and supratherapeutic TLs were found in 38% and 23% of children, respectively. ATIs were detected in four patients. A correlation was found between IFX TL and CRP [rs

= -0.51; p < 0.01] and FC [rs = -0.49; p < 0.01]. However, when only clinical disease activity was considered, no difference in median TL was found between remission and active disease (resp. 3.5 microg/ml [IQR 2-5] and 2.3 microg/ml [IQR 0.3-4.6]; p = 0.2).
Conclusions: IFX TLs are related to biochemical markers of disease activity. This could provide a rationale for monitoring TLs in children receiving IFX for IBD.

Gepubliceerd: Scand J Gastroenterol 2015 Sep;50(9):1110-7
Impact factor: 2.361

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4. Experience with Molecular Adsorbents Recirculation System Treatment in Twenty Children Listed for High Urgency Liver Transplantation
Lexmond WS, Van Dael CM, Scheenstra R, Goorhuis JF, Sieders E, Verkade HJ, Van Rheenen PF, Komhoff M

For over 10 years, children in our national center for pediatric liver transplantation have been treated with Molecular Adsorbent Recirculation System (MARS) liver dialysis as a bridging therapy to high urgency liver transplantation. Treatment was reserved for 20 patients with the highest degrees of hepatic encephalopathy (median grade 3.5), in whom death from neurological sequelae was considered imminent, which was further reflected in significantly higher INR, ammonia levels and worse prognostic liver indexes (MELD/PELD and Liver Injury Units) than in 32 waitlisted patients who did not receive MARS dialysis. MARS therapy was generally well tolerated, with a reduction in thrombocytes and hemorrhage as most common side effects. Improvement of hepatic encephalopathy was documented in 30% of treated patients, but progression to grade IV encephalopathy occurred in 45% of patients despite treatment. Serum ammonia, bilirubin, bile acids and creatinine significantly decreased during treatment. 80% of MARS treated patients survived to undergo liver transplantation, and survival was equivalent to that of non-MARS-treated patients with severe liver failure (69%, p=0.52). The heterogeneity between MARS-treated and -untreated patients in our cohort precludes the statistical evaluation of a benefit of MARS on patient survival. Our data demonstrate safety of MARS even in the most severely ill patients awaiting liver transplantation, but strategies that promote a more rapid and widespread availability of high-quality donor organs remain of critical importance for improving patient survival in cases of severe acute liver failure.

Gepubliceerd: Liver Transpl 2015;21(3):369-80
Impact factor: 4.241

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5. Human buccal epithelium acquires microbial hyporesponsiveness at birth, a role for secretory leukocyte protease inhibitor
Menckeberg CL, Hol J, Simons-Oosterhuis Y, Raatgeep HR, de Ruiter LF, Lindenbergh-Kortleve DJ, Korteland-van Male AM, El AS, van Lierop PP, Kleerebezem M, Groeneweg M, Kraal G, Elink-Schuurman BE, de Jongste JC, Nieuwenhuis EE, Samsom JN

Objective: Repetitive interaction with microbial stimuli renders epithelial cells (ECs) hyporesponsive to microbial stimulation. Previously, we have reported that buccal ECs from a subset of paediatric patients with Crohn's disease are not hyporesponsive and spontaneously released chemokines. We now aimed to identify kinetics and mechanisms of acquisition of hyporesponsiveness to microbial stimulation using primary human buccal epithelium.
Design: Buccal ECs collected directly after birth and in later stages of life were investigated. Chemokine release and regulatory signalling pathways were studied using primary buccal ECs and the buccal EC line TR146. Findings were extended to the intestinal mucosa using murine model systems.
Results: Directly after birth, primary human buccal ECs spontaneously produced the chemokine CXCL-8 and were responsive to microbial stimuli. Within the first weeks of life, these ECs attained hyporesponsiveness, associated with inactivation of the NF-kappaB pathway and upregulation of the novel NF-kappaB inhibitor SLPI but no other known NF-kappaB inhibitors. SLPI protein was abundant in the cytoplasm and the nucleus of hyporesponsive buccal ECs. Knock-down of SLPI in TR146-buccal ECs induced loss of hyporesponsiveness with increased NF-kappaB activation and subsequent chemokine release. This regulatory mechanism extended to the intestine, as colonisation of germfree mice elicited SLPI expression in small intestine and colon. Moreover, SLPI-deficient mice had increased chemokine expression in small intestinal and colonic ECs.
Conclusions: We identify SLPI as a new player in acquisition of microbial hyporesponsiveness by buccal and intestinal epithelium in the first weeks after microbial colonisation.

Gepubliceerd: Gut 2015 Jun;64(6):884-93
Impact factor: 14.660

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6. Protective effect of a low single dose inhaled steroid against exercise induced bronchoconstriction
Visser R, Wind M, de Graaf B, de Jongh FH, van der Palen J, Thio BJ

Objective: Daily use of inhaled corticosteroids (ICS) reduces exercise induced bronchoconstriction (EIB) in asthmatic children. A high single dose of ICS also provided acute protection against EIB. Objective of this study is to investigate whether a low single dose of ICS offers protection against EIB in asthmatic children.
Methods: 31 Mild asthmatic children not currently treated with inhaled corticosteroids, 5-16 years, with EIB (fall in FEV0.5/1 >/= 13%) were included in a prospective intervention study. They performed two ECT's within 2 weeks. Four hours before the second test children inhaled 200 mug beclomethasone-dipropionate (BDP) with a breath-actuated inhaler (BAI).
Results: The median fall in FEV0.5/1 after 200 mug BDP was significantly reduced from 30.9% at baseline to 16.0% (P < 0.001). Twenty children (64.5%) showed a good response to 200 mug BDP (>/=50% decrease in fall of FEV0.5/1), while 8 children showed a moderate response (25-50%), and three children showed no response at all (< 25%).

Conclusion: A low single dose ICS offers acute protection against EIB in the majority of asthmatic children not currently treated with inhaled corticosteroids. Pediatr Pulmonol.

Gepubliceerd: Pediatr Pulmonol 2015;50(12):1178-83
Impact factor: 2.704

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7. Reversibility after inhaling salbutamol in different body postures in asthmatic children: A pilot study
Visser R, van der Palen J, de Jongh FH, Thio BJ

Rationale: Pulmonary medication is mostly delivered in the form of medical aerosols to minimize systemic side effects. A major drawback of inhaled medication is that the majority of inhaled particles impacts in the oropharynx at the sharp bend of the airway. Stretching the airway by a forward leaning body posture with the neck extended ("sniffing position") may improve pulmonary deposition and clinical effects.
Methods: 41 asthmatic children who were planned for standard reversibility testing at the pulmonary function lab, alternately inhaled 200 mugr salbutamol with an Autohaler((R)) in the standard or in the forward leaning body posture. Forced Expiratory Volume in 1 s (FEV1), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF), Mean Expiratory Flow at 25% of vital capacity (MEF25) and Mean Expiratory Flow at 75% of vital capacity (MEF75) were analysed.
Results: The children in the forward leaning body posture group showed a significantly higher mean FEV1 reversibility than the control group after inhalation of 200 mugr salbutamol (10.2% versus 4.1%, p = 0.019). Additionally, mean MEF75 was significantly more reversible in the forward leaning body posture group versus the standard body posture group (32.2% resp. 8.9%, p = 0.013).
Conclusion: This pilot study showed a higher reversibility of FEV1 and MEF75 after inhaling salbutamol in a forward leaning body posture compared to the standard body posture in asthmatic children. This suggests that pulmonary effects of salbutamol can be improved by inhaling in a forward leaning body posture with the neck extended. This effect is possibly due to a higher pulmonary deposition of salbutamol and should be confirmed in a randomized controlled trial.

Gepubliceerd: Respir Med 2015 Apr;109(4):459-62
Impact factor: 3.086

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8. Reversibility of pulmonary function after inhaling salbutamol in different doses and body postures in asthmatic children
Visser R, Kelderman S, de Jongh FH, van der Palen J, Thio BJ

Rationale: Pulmonary medication is often delivered in the form of medical aerosols designed for inhalation. Recently, breath actuated inhalers (BAI's) gained popularity as they can be used without spacers. A major drawback of BAI's is the impaction in the upper airway. Stretching the upper airway by a forward leaning body posture with the neck extended ("sniffing position") during inhalation may reduce upper

airway impaction and improve pulmonary deposition. Aim of this study was to investigate the reversibility of lung function with different doses salbutamol inhaled with a BAI in the forward leaning posture compared to the standard posture in asthmatic children.
Methods: 22 clinically stable asthmatic children, 5-14 years old, performed four reversibility measurements. Children inhaled 200 mug or 400 mug salbutamol with a BAI in the standard or in the forward leaning posture with the neck extended in a randomized single-blinded cross-over design.
Results: Reversibility of lung function after inhaling salbutamol in the forward leaning posture was not significantly different compared to inhalation in the standard posture. Mean FEV1 reversibility was significantly greater after inhaling 400 mug salbutamol compared to 200 mug salbutamol in the standard posture (9.4% +/- 9.5% versus 4.5% +/- 7.5%, difference 4.9% (95CI 0.9; 9.0%); p = 0.021).
Conclusion: In clinically stable asthmatic children, inhalation of salbutamol with a BAI in a forward leaning posture does not increase reversibility of lung function. Inhalation of 400 mug compared to 200 mug salbutamol with a BAI does improve reversibility.

Gepubliceerd: Respir Med 2015 Jul 23;109(10):1274-9
Impact factor: 3.086

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9. The effect of body posture during medication inhalation on exercise induced bronchoconstriction in asthmatic children
Visser R, Wind M, de Graaf BJ, de Jongh FH, van der Palen J, Thio BJ

Rationale: Inhaling medication in a standard body posture leads to impaction of particles in the sharp angle of the upper airway. Stretching the upper airway by extending the neck in a forward leaning body posture may improve pulmonary deposition. A single dose of inhaled corticosteroids (ICS) offers acute, but moderate protection against exercise induced bronchoconstriction (EIB). This study investigated whether inhaling a single dose of ICS in a forward leaning posture improves this protection against EIB.
Methods: 32 Asthmatic children, 5-16 years, with EIB (Median fall in FEV1 or FEV0.5 30.9%) performed two exercise challenge tests (ECT's) with spirometry in a single blinded cross-over trial design. Children inhaled a single dose of 200 mug beclomethasone dipropionate (BDP) 4 h before the ECT, once in the standard posture and once with the neck extended in a forward leaning posture. Spirometry was also performed before the inhalation of the single dose of BDP.
Results: Inhalation of BDP in both body postures provided similar protection against EIB (fall in FEV1 or FEV0.1 in standard posture 16.7%; in forward leaning posture 15.1%, p = 0.83). Inhaling ICS in a forward leaning posture significantly delayed EIB compared to inhaling in the standard posture (respectively 2.5 min +/- 1.0 min vs. 1.6 min +/- 0.8 min; difference 0.9 min (95CI 0.25; 1.44 min); p = 0.01).
Conclusion: Inhalation of a single dose BDP in both the forward leaning posture and the standard posture provided effective and similar protection against EIB in asthmatic children, but the forward leaning posture resulted in a delay of EIB.
Register: NTR3432 (www.trialregister.nl).

Respir Med 2015 Oct;109(10):1257-61
Impact factor: 3.086

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10. The impact of discussing exercise test results of young asthmatic children on adherence to maintenance medication
Visser R, Brusse-Keizer M, van der Palen J, Klok T, Thio BJ

Objective: Parents' awareness of their child's asthma may improve by discussing an exercise challenge test (ECT) result with them. We investigated the influence of discussing an ECT result with parents on adherence to inhaled maintenance medication, parental illness perceptions and medication beliefs in young asthmatic children.
Methods: A total of 79 children, 4-7 years old and enrolled in our standard comprehensive asthma care program, performed an ECT to assess exercise induced bronchoconstriction (EIB). The result of the ECT was immediately discussed with the parents. Median medication adherence level was measured with electronic medication loggers from six weeks before the ECT till six weeks afterwards. Parental beliefs about medicines and illness perceptions were measured with the Beliefs about Medicines Questionnaire (BMQ) and the Brief Illness Perceptions Questionnaire (B-IPQ).
Results: The median baseline adherence level was high (83%) and showed a small significant decline after the ECT. There was no significant difference in the decrease in median adherence level between the children with or without EIB. Most parents (82.1%) showed a positive necessity-concern ratio at baseline, as measured with the BMQ. There was no clinical relevant change in medication concerns and necessity scores or in illness perceptions.
Conclusion: Discussing ECT results with parents does not modify median adherence levels to inhaled maintenance medication nor medication beliefs of highly adherent young asthmatic children who are already enrolled in a comprehensive asthma care program.

Gepubliceerd: J Asthma 2015 May 18;52(7):743-8
Impact factor: 1.802

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11. Emphasizing of shaking the inhaler as part of inhalation instruction is important in young asthmatic children
Visser R, Brusse-Keizer MG, van der Palen J, Thio BJ

Background: Current guidelines recommend to monitor inhalation technique in asthmatic children every 3-6 months. The aim of this study was to investigate inhalation technique 6 weeks after instruction in young asthmatic children, using a pressurized metered dose inhaler with spacer.
Methods: 91 asthmatic children, 4-8 years, from our outpatient clinic, demonstrated their inhalation technique with a pressurized metered dose inhaler with spacer. Errors in inhalation technique were scored on an inhaler specific standardized

checklist designed by the Dutch Lung Foundation. Afterwards, feedback on inhalation technique was provided to the child and his/her parent(s). Six weeks later their inhalation technique was reevaluated.
Results: Significantly more children carried out a perfect inhalation technique (67.0% vs. 36.3%, p=<0.001) and significantly less children showed one, two or three errors (31.5% vs. 63.7% p=<0.001) 6 weeks after instruction. Significantly more children failed to shake their inhaler 6 weeks after instruction (16.9% vs. 6.6%, p=0.035).
Conclusion: Although we observed a significant improvement in inhalation technique six weeks after instruction with tailored feedback, more young asthmatic children failed to shake their inhaler. We recommend that reinforcement on essential steps that are performed correctly should be highly emphasized.

Pediat Therapeut 2015;5(2):244
Impact factor: 0.314

Totale impact factor: 43.885
Gemiddelde impact factor: 3.990

Aantal artikelen 1e, 2e of laatste auteur: 6
Totale impact factor: 14.078
Gemiddelde impact factor: 2.346

Klinische Chemie

1. Identification of a human synaptotagmin-1 mutation that perturbs synaptic vesicle cycling
Baker K, Gordon SL, Grozeva D, van Kogelenberg M, Roberts NY, Pike M, Blair E, Hurles ME, Chong WK, Baldeweg T, Kurian MA, Boyd SG, Cousin MA, Raymond FL

Synaptotagmin-1 (SYT1) is a calcium-binding synaptic vesicle protein that is required for both exocytosis and endocytosis. Here, we describe a human condition associated with a rare variant in SYT1. The individual harboring this variant presented with an early onset dyskinetic movement disorder, severe motor delay, and profound cognitive impairment. Structural MRI was normal, but EEG showed extensive neurophysiological disturbances that included the unusual features of low-frequency oscillatory bursts and enhanced paired-pulse depression of visual evoked potentials. Trio analysis of whole-exome sequence identified a de novo SYT1 missense variant (I368T). Expression of rat SYT1 containing the equivalent human variant in WT mouse primary hippocampal cultures revealed that the mutant form of SYT1 correctly localizes to nerve terminals and is expressed at levels that are approximately equal to levels of endogenous WT protein. The presence of the mutant SYT1 slowed synaptic vesicle fusion kinetics, a finding that agrees with the previously demonstrated role for I368 in calcium-dependent membrane penetration. Expression of the I368T variant also altered the kinetics of synaptic vesicle endocytosis. Together, the clinical features, electrophysiological phenotype, and in vitro neuronal phenotype associated with this dominant negative SYT1 mutation highlight presynaptic mechanisms that mediate human motor control and cognitive development.

Gepubliceerd: J Clin Invest 2015 Apr 1;125(4):1670-8
Impact factor: 13.262

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2. Adult-onset congenital thrombotic thrombocytopenic purpura caused by a novel compound heterozygous mutation of the ADAMTS13 gene
Krabbe JG, Kemna EW, Strunk AL, Jobse PA, Kramer PA, Dikkeschei LD, van den Heuvel LP, Fijnheer R, Verdonck LF

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease, characterized by microangiopathic hemolytic anaemia and thrombocytopenia, resulting in neurologic and/or renal abnormalities. We report a 49-year-old patient with a history of thrombotic events, renal failure, and thrombocytopenia. Blood analysis demonstrated no ADAMTS13 activity in the absence of antibodies against ADAMTS13. The complete ADAMTS13 gene was sequenced, and two mutations were identified: one mutation on exon 24 (Arg1060Asp), which had previously been described, and a mutation on exon 27 (Met1260IlefsX34), which has not been reported. For these mutations, compound heterozygosity appears to be necessary to cause TTP, as family members of the patient display only one of the mutations and all displayed normal ADAMTS13 activity.

Gepubliceerd: Int J Hematol 2015 Aug 13;102(4):477-81
Impact factor: 1.918

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3. Successful treatment of fulminant postoperative bleeding due to acquired haemophilia
Mekenkamp LJ, Beishuizen A, Slomp J, Legdeur MC, Klaase JM, Trof RJ

Acquired haemophilia is a rare but life-threatening phenomenon in patients who have undergone surgical treatment. We describe a patient with a history of pancreatic cancer and a conventional pancreaticoduodenectomy, who underwent elective resection of an enterocutaneous fistula, complicated by fulminant haemorrhagic shock, caused by acquired haemophilia A. Eventually, the bleeding was controlled by a combination of aggressive haemostatic and immunosuppressive therapy. Prompt diagnosis of acquired haemophilia is crucial to allow early and appropriate haemostatic treatment and reduce the period of increased bleeding risk by eradicating the inhibitor with immunosuppressive therapy.

Gepubliceerd: Neth J Med 2015 May;73(4):182-6
Impact factor: 1.969

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4. Circulating tumor cells before and during follow-up after breast cancer surgery
van Dalum G, van der Stam GJ, Tibbe AG, Franken B, Mastboom WJ, Vermes I, de Groot MR, Terstappen LW

The presence of circulating tumor cells (CTC) is an independent prognostic factor for progression-free and overall survival for patients with metastatic and newly diagnosed breast cancer. The present study was undertaken to explore whether the presence of CTC before and during follow-up after surgery is associated with recurrence free survival (RFS) and overall survival (OS). In a prospective single center study, CTC were enumerated with the CellSearch system in 30 ml of peripheral blood of 403 stage I-III patients before undergoing surgery for breast cancer (A) and if available 1 week after surgery (B), after adjuvant chemo- and/or radiotherapy or before start of long-term hormonal therapy (C), one (D), two (E) and three (F) years after surgery. Patients were stratified into unfavorable (CTC >/=1) and favorable (CTC=0) prognostic groups. >1 CTC in 30 ml blood was detected in 75/403 (19%) at A, 66/367 (18%) at B, 40/263 (15%) at C, 30/235 (12%) at D, 18/144 (11%) at E and 11/83 (13%) at F. RFS and OS was significantly lower for unfavorable CTC as compared to favorable CTC before surgery (p=0.022 and p=0.006), after adjuvant therapy (p<0.001 and p=0.018) and one (p=0.006 and p=0.013) and two (p<0.001 and p=0.045) years after surgery, but not 1 week post-surgery. The presence of CTC in blood drawn pre and one and two years after surgery, but not post-surgery is associated with shorter RFS and OS for stage I-III breast cancer.

Gepubliceerd: Int J Oncol 2015 Oct 6;46(1):407-13
Impact factor: 3.025

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5. Importance of circulating tumor cells in newly diagnosed colorectal cancer
van Dalum G, Stam GJ, Scholten LF, Mastboom WJ, Vermes I, Tibbe AG, de Groot MR, Terstappen LW

Presence of circulating tumor cells (CTC) is associated with poor prognosis in patients with metastatic colorectal cancer (CRC). The present study was conducted to determine if the presence of CTC prior to surgery and during followup in patients with newly diagnosed non-metastatic CRC can identify patients at risk for disease recurrence. In a prospective single center study 183 patients with newly diagnosed non-disseminated CRC, scheduled for surgery, were enrolled and followed-up for a median of 5.1 years. CTC were enumerated with the CellSearch system in 4 aliquots of 7.5 ml of blood before surgery and at several time-points during follow-up after surgery. The results showed that >/=1 CTC/30 ml of blood were detected in 44 (24%) patients before surgery. Patients with CTC before surgery had a significant decrease in recurrence-free survival (RFS, log-rank test p=0.014) and colon cancer related survival (CCRS, p=0.002). The 5-year RFS dropped from 75 to 61% and the 5-year CCRS from 83 to 69% for patients with CTC before surgery. The presence of CTC and positive lymph nodes remained significant factors in multivariate analysis for recurrence-free survival (RFS). Surprisingly, the presence of CTC weeks after surgery was not significantly associated with RFS and CCRD whereas CTC 2-3 years after surgery was again significantly associated with RFS and CCRD. The presence of CTC in patients with stage I-III CRC before surgery is associated with a significant reduction in RFS and CCRS. These findings suggest a role of CTC detection to assess which patients need adjuvant treatment.

Gepubliceerd: Int J Oncol 2015 Mar;46(3):1361-8
Impact factor: 3.025

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6. Diverse phenotypic consequences of mutations affecting the C-terminus of FLNA
van Kogelenberg M, Clark AR, Jenkins Z, Morgan T, Anandan A, Sawyer GM, Edwards M, Dudding T, Homfray T, Castle B, Tolmie J, Stewart F, Kivuva E, Pilz DT, Gabbett M, Sutherland-Smith AJ, Robertson SP

Filamin A, the filamentous protein encoded by the X-linked gene FLNA, cross-links cytoskeletal actin into three-dimensional networks, facilitating its role as a signalling scaffold and a mechanosensor of extrinsic shear forces. Central to these functions is the ability of FLNA to form V-shaped homodimers through its C-terminal located filamin repeat 24. Additionally, many proteins that interact with FLNA have a binding site that includes the C-terminus of the protein. Here, a cohort of patients with mutations affecting this region of the protein is studied, with particular emphasis on the phenotype of male hemizygotes. Seven unrelated families are reported, with five exhibiting a typical female presentation of periventricular heterotopia (PH), a

neuronal migration disorder typically caused by loss-of-function mutations in FLNA. One male presents with widespread PH consistent with previous male phenotypes attributable to hypomorphic mutations in FLNA. In stark contrast, two brothers are described with a mild PH presentation, due to a missense mutation (p.Gly2593Glu) inserting a large negatively charged amino acid into the hydrophobic dimerisation interface of FLNA. Co-immunoprecipitation, in vitro cross-linking studies and gel filtration chromatography all demonstrated that homodimerisation of isolated FLNA repeat 24 is abolished by this p.Gly2593Glu substitution but that extended FLNAGly2593Glu repeat 16-24 constructs exhibit dimerisation. These observations imply that other interactions apart from those mediated by the canonical repeat 24 dimerisation interface contribute to FLNA homodimerisation and that mutations affecting this region of the protein can have broad phenotypic effects. KEY MESSAGES: * Mutations in the X-linked gene FLNA cause a spectrum of syndromes. * Genotype-phenotype correlations are emerging but still remain unclear. * C-term mutations can confer male lethality, survival or connective tissue defects. * Mutations leading to the latter affect filamin dimerisation. * This deficit is compensated for by remotely acting domains elsewhere in FLNA.

Gepubliceerd: J Mol Med (Berl) 2015 Feb 18;93(7):773-82
Impact factor: 5.107

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7. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data

Wright CF, Fitzgerald TW, Jones WD, Clayton S, McRae JF, van Kogelenberg M, King DA, Ambridge K, Barrett DM, Bayzetinova T, Bevan AP, Bragin E, Chatzimichali EA, Gribble S, Jones P, Krishnappa N, Mason LE, Miller R, Morley KI, Parthiban V, Prigmore E, Rajan D, Sifrim A, Swaminathan GJ, Tivey AR, Middleton A, Parker M, Carter NP, Barrett JC, Hurles ME, FitzPatrick DR, Firth HV

Background: Human genome sequencing has transformed our understanding of genomic variation and its relevance to health and disease, and is now starting to enter clinical practice for the diagnosis of rare diseases. The question of whether and how some categories of genomic findings should be shared with individual research participants is currently a topic of international debate, and development of robust analytical workflows to identify and communicate clinically relevant variants is paramount.
Methods: The Deciphering Developmental Disorders (DDD) study has developed a UK-wide patient recruitment network involving over 180 clinicians across all 24 regional genetics services, and has performed genome-wide microarray and whole exome sequencing on children with undiagnosed developmental disorders and their parents. After data analysis, pertinent genomic variants were returned to individual research participants via their local clinical genetics team.
Findings: Around 80,000 genomic variants were identified from exome sequencing and microarray analysis in each individual, of which on average 400 were rare and predicted to be protein altering. By focusing only on de novo and segregating variants in known developmental disorder genes, we achieved a diagnostic yield of 27% among 1133 previously investigated yet undiagnosed children with

developmental disorders, whilst minimising incidental findings. In families with developmentally normal parents, whole exome sequencing of the child and both parents resulted in a 10-fold reduction in the number of potential causal variants that needed clinical evaluation compared to sequencing only the child. Most diagnostic variants identified in known genes were novel and not present in current databases of known disease variation.
Interpretation: Implementation of a robust translational genomics workflow is achievable within a large-scale rare disease research study to allow feedback of potentially diagnostic findings to clinicians and research participants. Systematic recording of relevant clinical data, curation of a gene-phenotype knowledge base, and development of clinical decision support software are needed in addition to automated exclusion of almost all variants, which is crucial for scalable prioritisation and review of possible diagnostic variants. However, the resource requirements of development and maintenance of a clinical reporting system within a research setting are substantial.
Funding: Health Innovation Challenge Fund, a parallel funding partnership between the Wellcome Trust and the UK Department of Health.

Gepubliceerd: Lancet 2015 Apr 4;385(9975):1305-14
Impact factor: 45.217

Totale impact factor: 73.523
Gemiddelde impact factor: 10.503

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 7.025
Gemiddelde impact factor: 3.513

Klinische Farmacie

1. Amoxicillin concentrations in relation to beta-lactamase activity in sputum during exacerbations of chronic obstructive pulmonary disease
Brusse-Keizer M, van der Valk PD, van der Zanden RW, Nijdam L, van der Palen J, Hendrix R, Movig K

Background: Acute exacerbations of chronic obstructive pulmonary disease (COPD) are often treated with antibiotics. Theoretically, to be maximally effective, the antibiotic concentration at sites of infection should exceed the minimum inhibitory concentration at which 90% of the growth of potential pathogens is inhibited (MIC90). A previous study showed that most hospitalized COPD patients had sputum amoxicillin concentrations <LMIC90 when treated with amoxicillin/clavulanic acid. Those with adequate sputum concentrations had better clinical outcomes. Low amoxicillin concentrations can be caused by beta-lactamase activity in the lungs. This study investigated whether patients with sputum amoxicillin concentrations <MIC90 had higher beta-lactamase activity in sputum than patients with a concentration >/=MIC90.
Methods: In total, 23 patients hospitalized for acute exacerbations of COPD and treated with amoxicillin/clavulanic acid were included. Sputum and serum samples were collected at day 3 of treatment to determine beta-lactamase activity in sputum and amoxicillin concentrations in both sputum and serum.
Results: We found no difference in beta-lactamase activity between patients with sputum amoxicillin concentrations <MIC90 and >/=MIC90 (P=0.79). Multivariate logistic regression analysis showed no significant relationship between beta-lactamase activity and sputum amoxicillin concentrations <MIC90 or >/=MIC90 (odds ratio 0.53; 95% confidence interval 0.23-1.2; P=0.13). Amoxicillin concentrations were <MIC90 in 78% of sputum samples and in 30% of serum samples.
Conclusion: In patients treated with amoxicillin/clavulanic acid for an acute exacerbation of COPD, sputum beta-lactamase activity did not differ between those with sputum amoxicillin concentrations <MIC90 or >/=MIC90. The finding that the majority of patients had sputum amoxicillin concentrations <MIC90 suggests that current treatment with antibiotics for acute exacerbations of COPD should be optimized.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis 2015;10:455-61
Impact factor: 3.141

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2. TGF-beta antibody uptake in recurrent high grade glioma imaged with 89Zr-fresolimumab PET
den Hollander MW, Bensch F, Glaudemans AW, Oude Munnink TH, Enting RH, den Dunnen WF, Heesters MA, Kruyt FA, Lub-de Hooge MN, de Groot JC, Pearlberg J, Gietema JA, de Vries EG, Walenkamp AM

Transforming growth factor-beta (TGF-beta) signaling is involved in glioma development. The monoclonal antibody fresolimumab (GC1008) can neutralize all mammalian isoforms of TGF-beta and tumor uptake can be visualized and quantified with 89Zr-fresolimumab PET in mice. The aim of this study was to investigate the fresolimumab uptake in recurrent high grade gliomas using 89Zr-fresolimumab PET and to assess treatment outcome in patients with recurrent high grade glioma treated with fresolimumab.
Methods: Patients with recurrent glioma were eligible. After intravenous administration of 37 megabecquerel (MBq) (5 mg) 89Zr-fresolimumab, PET scans were acquired on day 2 and/or day 4 after tracer injection. Thereafter, patients were treated with 5 mg/kg fresolimumab intravenously every 3 weeks. 89Zr-fresolimumab tumor uptake was quantified as maximum standardized uptake value (SUVmax). MRI scans for response evaluation were performed after 3 infusions or as clinically indicated.
Results: Included were 12 recurrent high grade glioma patients: ten glioblastoma, one anaplastic oligodendroglioma and one anaplastic astrocytoma. All patients underwent an 89Zr-fresolimumab PET scan 4 days after injection. In four patients an additional PET scan was performed on day 2 after injection. SUVmax on day 4 in tumor lesions was 4.6 (1.5 - 13.9) versus a median SUVmean of 0.3 (0.2 - 0.5) in normal brain tissue. All patients showed clinical and/or radiological progression after 1-3 infusions fresolimumab. Median progression free survival was 61 days (25-80) and median overall survival 106 days (37-417).
Conclusion: 89Zr-fresolimumab penetrated recurrent high grade gliomas very well, however this did not result in clinical benefit.

Gepubliceerd: J Nucl Med 2015 Jul 1;56(9):1310-4
Impact factor: 6.160

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3. Differences in Adherence to Common Inhaled Medications in COPD
Koehorst-Ter Huurne K, Movig K, van der Valk PD, van der Palen J, Brusse-Keizer M

Objective: To study differences in adherence to common inhaled medications in COPD.
Methods: Adherence of 795 patients was recorded from pharmacy records over 3 years in the COMIC cohort. It was expressed as percentage and deemed good at >/=75-</=125%, sub-optimal >/=50-<75%, and poor <50% (underuse) or >125% (overuse). Most patients used more than one medication, so we present 1379 medication periods.
Results: The percentages of patients with good therapy adherence ranged from 43.2 (beclomethasone) -75.8% (tiotropium); suboptimal from 2.3 (budesonide) -23.3% (fluticasone); underuse from 4.4 (formoterol/budesonide) -18.2% (beclomethasone); and overuse from 5.1 (salmeterol) -38.6% (budesonide). Patients using fluticasone or salmeterol/fluticasone have a 2.3 and 2.0-fold increased risk of suboptimal versus good adherence compared to tiotropium. Patients using salmeterol/fluticasone or beclomethasone have a 2.3- and 4.6-fold increased risk of underuse versus good adherence compared to tiotropium. Patients using

budesonide, salmeterol/fluticasone, formoterol/budesonide, ciclesonide and beclomethasone have an increased risk of overuse versus good adherence compared to tiotropium. Adherence to inhalation medication is inversely related to lung function.
Conclusion: Therapy adherence to inhalation medication for the treatment of COPD is in our study related to the medication prescribed. Tiotropium showed the highest percentage of patients with good adherence, followed by ciclesonide, both dosed once daily. The idea of improving adherence by using combined preparations cannot be confirmed in this study. Further research is needed to investigate the possibilities of improving adherence by changing inhalation medication.

Gepubliceerd: COPD 2015 Mar 16;12(6):643-8
Impact factor: 2.673

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4. Safety and tolerability of nebulized amoxicillin + clavulanic acid in patients with stable COPD
Nijdam LC, Kuijvenhoven JC, van der Valk PD, Brusse-Keizer MG, van der palen J, Movig KL

Objective: To study the safety and tolerability of nebulized amoxicillin + clavulanic acid in patients with stable copd. Acute exacer- bations in copd are often treated with antibiotics. Previous studies showed ineffective amoxicillin concentrations in sputum in two thirds of the patients treated with systemic amoxicillin + clavulanic acid. Local administration, theo r- etically providing higher concentrations, has not been described before.
Design: Prospective observational intervention study.
Methods: Nine subjects received ascending doses amoxicillin + clavulanic acid, ranging from 50 + 10 mg up to 300 + 60 mg. Plasma and expectorated sputum samples were assayed for amoxicillin content. Safety was evaluated by spirometry before and after nebulization. Tolerability was evaluated by questionnaire.
Results: Spirometry showed no clinically relevant reduction in fev1 after nebulization with amoxicillin + clavulanic acid. In 34 nebulizations only 3 mild adverse events occurred. The sputum amoxicillin quantification showed levels well above mic90, while no effective levels were found in plasma.
Conclusion: Inhalation of nebulized amoxicillin + clavulanic acid is safe and well tolerated. Nebulized amoxicillin + clavulanic acid produces sputum concentrations well above mic with low systemic exposure.

Gepubliceerd: PW Wetenschappelijk Platform. 2015;9:a1510
Impact factor: 0

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5. 89Zr-bevacizumab PET Visualizes Heterogeneous Tracer Accumulation in Tumor Lesions of Renal Cell Carcinoma Patients and Differential Effects of Anti-angiogenic Treatment

Oosting SF, Brouwers AH, van Es SC, Nagengast WB, Oude Munnink TH, Lub-de Hooge MN, Hollema H, de Jong JR, de Jong IJ, de Haas S, Scherer SJ, Sluiter WJ, Dierckx RA, Bongaerts AH, Gietema JA, de Vries EG

No validated predictive biomarkers for anti-angiogenic treatment of metastatic renal cell carcinoma (mRCC) exist. Tumor vascular endothelial growth factor A (VEGF-A) level may be useful. We determined tumor uptake of 89Zr-bevacizumab, a VEGF-A-binding positron-emission-tomography (PET) tracer, in mRCC patients before and during anti-angiogenic treatment in a pilot study.
Methods: Patients underwent 89Zr-bevacizumab PET scans at baseline and 2 and 6 weeks after initiating either bevacizumab (10 mg/kg every 2 weeks, n = 11) with interferon-alpha 3-9 million IU 3x/week, or sunitinib (50 mg daily, 4 of every 6 weeks, n = 11). Standardized uptake values (SUV) were compared to plasma VEGF-A and time to disease progression.
Results: 89Zr-bevacizumab PET scans visualized 125 evaluable tumor lesions in 22 patients with a median SUVmax of 6.9 (range 2.3-46.9). Bevacizumab/interferon-alpha induced a mean change in tumor SUVmax of -47.0% (range -84.7 to +20.0%, $P < 0.0001$) at 2 weeks and an additional -9.7% (range -44.8 to +38.9%, $P = 0.015$) at 6 weeks. In the sunitinib group the mean change in tumor SUVmax was -14.3% at 2 weeks (range -80.4 to +269.9, $P = 0.006$), but at 6 weeks the mean change in tumor SUVmax was +72.6% (range -46.4 to +236%, $P < 0.0001$) above baseline. SUVmax was not related to plasma VEGF-A at all scan moments. Baseline mean tumor SUVmax > 10.0 in the three most intense lesions corresponded with longer time to disease progression (89.7 versus 23.0 weeks, hazard ratio 0.22, 95% CI 0.05-1.00).
Conclusion: Tumor uptake of 89Zr-bevacizumab is high in mRCC with remarkable inter-patient and intra-patient heterogeneity. Bevacizumab/interferon-alpha strongly decreases tumor uptake whereas sunitinib results in a modest reduction with an overshoot after 2 drug-free weeks. High baseline tumor SUVmax was associated with longer time to progression.

Gepubliceerd: J Nucl Med 2015;56(1):63-9
Impact factor: 6.160

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6. Agranulocytosis and septic shock after metamizole use
Oude Munnink TH, Annink-Smoors M, Hom HW, Sportel ET

Background: Metamizole is an analgesic, the orally administered form of which was withdrawn in the Netherlands in 1989 due to an unacceptably high incidence of agranulocytosis. However, later studies showed a much lower incidence and since 2013 the use of metamizole has been recommended by the national guideline on postoperative pain.
Case description: A 58-year-old woman was referred by her general practitioner to our hospital with suspected diverticulitis. Three days previously the patient had returned from a four-week period of rehabilitation at a German spa following hip replacement surgery. She had been using metamizole since the operation. Within hours of admission, the patient developed septic shock and was transferred to the

intensive care unit. Laboratory tests revealed severe neutropenia of 0.2 x 109/l. Treatment consisted of filgrastim, piperacillin/tazobactam and haemodynamic support. After five days the patient was sufficiently recovered to return to the ward. **Conclusion:** Metamizole-related agranulocytosis is rare but potentially life-threatening. This condition is expected to occur more frequently as the use of metamizole in the Netherlands increases.

Gepubliceerd: Ned Tijdschr Geneeskd 2015;160:A9464
Impact factor: 0

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7. A versatile electrophoresis-based self-testplatform
Staal S, Ungerer M, Floris A, Brinke HT, Helmhout R, Tellegen M, Janssen K, Karstens E, van Arragon C, Lenk S, Staijen E, Bartholomew J, Krabbe H, Movig K, Dubsky P, van den Berg A, Eijkel J

This paper reports on recent research creating a family of electrophoresis-based point of care devices for the determination of a wide range of ionic analytes in various sample matrices. These devices are based on a first version for the point-of-care measurement of Li+ , reported in 2010 by Floris et al. (Lab. Chip 10 (2010)). With respect to this device, significant improvements inaccuracy,precision, detection limit and reliability have been obtained especiallyby the use of multiple injectionsof one sample on a single chip and integrated data-analysis. Internal and external validation by clinical laboratories for the determination of analytes in real patientsby a self-test is reported. For Li+ in blood better precisionthan the standard clinical determination for Li+ was achieved. For Na+ in human urine the method was found to be within the clinical acceptability limits. In a veterinary application, Ca2+ and Mg2+ were determined in bovine blood by means of the same chip, but using a different platform. Finally, promising preliminary results with the Medimate platform for the determination of creatinine in whole blood and quantification of both cations and anions through replicate measurements on the same sample with the same chip.

Gepubliceerd: Electrophoresis 2015;36(5):712-21
Impact factor: 3.028

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8. Traceability of biologicals: present challenges in pharmacovigilance
Vermeer NS, Spierings I, Mantel-Teeuwisse AK, Straus SM, Giezen TJ, Leufkens HG, Egberts TC, De Bruin ML

Introduction: Traceability is important in the postmarketing surveillance of biologicals, since changes in the manufacturing process may give rise to product- or batch-specific risks. With the expected expansion of the biosimilar market, there have been concerns about the ability to trace individual products within pharmacovigilance databases.
Areas covered: The authors discuss the present challenges in the traceability of biologicals in relation to pharmacovigilance, by exploring the processes involved in

ensuring traceability. They explore both the existing systems that are in place for the recording of exposure information in clinical practice, as well as the critical steps involved in the transfer of exposure data to various pharmacovigilance databases. **Expert opinion:** The existing systems ensure the traceability of biologicals down to the manufacturer within pharmacy records, but do not support the routine recording of batch information. Expected changes in supply chain standards provide opportunities to systematically record detailed exposure information. Spontaneous reporting systems are the most vulnerable link in ensuring traceability, due to the manual nature of data transfer. Efforts to improve the traceability should, in the short term, be focused toward encouraging health professionals and patients to systematically record and report detailed exposure information. Long-term solutions lie in expanding the accessibility to, and increasing the electronic exchange of exposure data.

Gepubliceerd: Expert Opin Drug Saf 2015 Jan;14(1):63-72
Impact factor: 2.911

Totale impact factor: 24.073
Gemiddelde impact factor: 3.009

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 5.814
Gemiddelde impact factor: 1.454

Medische Techniek

1. Controlled aggregation of primary human pancreatic islet cells leads to glucose-responsive pseudoislets comparable to native islets
Hilderink J, Spijker S, Carlotti F, Lange L, Engelse M, van Blitterswijk C, de Koning E, Karperien M, van Apeldoorn A

Clinical islet transplantation is a promising treatment for patients with type 1 diabetes. However, pancreatic islets vary in size and shape affecting their survival and function after transplantation because of mass transport limitations. To reduce diffusion restrictions and improve islet cell survival, the generation of islets with optimal dimensions by dispersion followed by reassembly of islet cells, can help limit the length of diffusion pathways. This study describes a microwell platform that supports the controlled and reproducible production of three-dimensional pancreatic cell clusters of human donor islets. We observed that primary human islet cell aggregates with a diameter of 100-150 mum consisting of about 1000 cells best resembled intact pancreatic islets as they showed low apoptotic cell death (<2%), comparable glucose-responsiveness and increasing PDX1, MAFA and INSULIN gene expression with increasing aggregate size. The re-associated human islet cells showed an a-typical core shell configuration with beta cells predominantly on the outside unlike human islets, which became more randomized after implantation similar to native human islets. After transplantation of these islet cell aggregates under the kidney capsule of immunodeficient mice, human C-peptide was detected in the serum indicating that beta cells retained their endocrine function similar to human islets. The agarose microwell platform was shown to be an easy and very reproducible method to aggregate pancreatic islet cells with high accuracy providing a reliable tool to study cell-cell interactions between insuloma and/or primary islet cells.

Gepubliceerd: J Cell Mol Med 2015 Aug;19(8):1836-46
Impact factor: 4.014

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2. Monitoring nutrient transport in tissue-engineered grafts
Liu J, Hilderink J, Groothuis TA, Otto C, van Blitterswijk CA, de Boer J

Limited nutrient diffusion in three-dimensional (3D) constructs is a major concern in tissue engineering. Therefore, monitoring nutrient availability and diffusion within a scaffold is an important asset. Since nutrients come in various forms, we have investigated the diffusion of the oxygen, luciferin and dextran molecules within tissue-engineered constructs using optical imaging technologies. First, oxygen availability and diffusion were investigated, using transgenic cell lines in which a hypoxia-responsive element drives expression of the green fluorescent protein gene. Using confocal imaging, we observed oxygen limitation, starting at around 200 microm from the periphery in the context of agarose gel with 1 million CHO cells. Diffusion of luciferin was monitored real-time in agarose gels using a cell line in which the luciferase gene was driven by a constitutively active CMV promoter. Gel

concentration affected the diffusion rate of luciferin. Furthermore, we assessed the diffusion rates of fluorescent dextran molecules of different molecular weights in biomaterials by fluorescence recovery after photobleaching (FRAP) and observed that diffusion depended on both molecular size and gel concentration. In conclusion, we have validated a set of efficient tools to investigate molecular diffusion of a range of molecules and to optimize biomaterials design in order to improve nutrient delivery.

Gepubliceerd: J Tissue Eng Regen Med 2015 Aug;9(8):952-60
Impact factor: 5.199

Totale impact factor: 9.213
Gemiddelde impact factor: 4.607

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 9.213
Gemiddelde impact factor: 4.607

Klinische Psychologie

1. Brain damage caused by exposure to organic solvents; diagnostics and disease course of chronic solvent-induced encephalopathy
van Valen E, van Hout MS, Wekking EM, Lenderink AF, van der Laan G, Hageman G

Since 1997 more than 3,000 patients have been referred to one of the two Dutch Solvent Teams with health problems that may have been caused by long-term occupational exposure to organic solvents.- A diagnosis of 'chronic solvent-induced encephalopathy' was made in approximately 500 patients.- The diagnostics of this disease is based on five elements: (a) symptoms in line with the diagnosis; (b) relevant exposure to an organic solvent with neurotoxic effects.

Gepubliceerd: Ned Tijdschr Geneeskd 2015;159:A9431
Impact factor: 0

Totale impact factor: 0
Gemiddelde impact factor: 0

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

KNO

1. Population-based prediction of fitting levels for individual cochlear implant recipients
van der Beek FB, Briaire JJ, Frijns JH

Objectives: This study analyzed the predictability of fitting levels for cochlear implant recipients based on a review of the clinical levels of the recipients.
Design: Data containing threshold levels (T-levels) and maximum comfort levels (M-levels) for 151 adult subjects using a CII/HiRes 90K cochlear implant with a HiFocus 1/1 J electrode were used. The 10th, 25th, 50th, 75th and 90th percentiles of the T- and M-levels are reported. Speech perception of the subjects, using a HiRes speech coding strategy, was measured during routine clinical follow-up.
Results: T-levels for most subjects were between 20 and 35% of their M-levels and were rarely (<1/50) below 10% of the M-levels. Furthermore, both T- and M-levels showed an increase over the first year of follow-up. Interestingly, levels expressed in linear charge units showed a clear increase in dynamic range (DR) over 1 year (29.8 CU; SD 73.0), whereas the DR expressed in decibels remained stable. T-level and DR were the only fitting parameters for which a significant correlation with speech perception ($r = 0.34$, $p < 0.01$, and $r = 0.33$, $p < 0.01$, respectively) could be demonstrated. Additionally, analysis showed that T- and M-level profiles expressed in decibels were independent of the subjects' across-site mean levels. Using mixed linear models, predictive models were obtained for the T- and M-levels of all separate electrode contacts.
Conclusions: On the basis of the data set from 151 subjects, clinically applicable predictive models for T- and M-levels have been obtained. Based on one psychophysical measurement and a population-based T- or M-level profile, individual recipients' T- and M-levels can be approximated with a closed-set formula. Additionally, the analyzed fitting level data can serve as a reference for future patients.

Gepubliceerd: Audiol Neurootol 2015;20(1):1-16
Impact factor: 1.705

Totale impact factor: 1.705
Gemiddelde impact factor: 1.705

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 1.705
Gemiddelde impact factor: 1.705

Laboratorium voor Microbiologie

1. Plasmid-mediated AmpC: prevalence in community-acquired isolates in Amsterdam, the Netherlands, and risk factors for carriage
Reuland EA, Halaby T, Hays JP, de Jongh DM, Snetselaar HD, van Keulen M, Elders PJ, Savelkoul PH, Vandenbroucke-Grauls CM, Al Naiemi N

Objectives: The objective of this study was to determine the prevalence of pAmpC beta-lactamases in community-acquired Gram negative bacteria in the Netherlands, and to identify possible risk factors for carriage of these strains.
Methods: Fecal samples were obtained from community-dwelling volunteers. Participants also returned a questionnaire for analysis of risk factors. Screening for pAmpC was performed with selective enrichment broth and a selective screening agar. Confirmation of AmpC-production was performed with two double disc combination tests: cefotaxime and ceftazidime with either boronic acid or cloxacillin as inhibitor. Multiplex PCR was used as gold standard for detection of pAmpC. 16S rRNA PCR and AFLP were performed as required, plasmids were identified by PCR-based replicon typing. Questionnaire results were analyzed with SPSS, version 20.0.
Results: Fecal samples were obtained from 550 volunteers; mean age 51 years (range: 18-91), 61% were females. pAmpC was present in seven E. coli isolates (7/550, 1.3%, 0.6-2.7 95% CI): six CMY-2-like pAmpC and one DHA. ESBL-encoding genes were found in 52/550 (9.5%, 7.3-12.2 95% CI) isolates; these were predominantly blaCTX-M genes. Two isolates had both ESBL and pAmpC. Admission to a hospital in the previous year was the only risk factor we identified.
Conclusions: Our data indicate that the prevalence of pAmpC in the community seems still low. However, since pAmpC-producing isolates were not identified as ESBL producers by routine algorithms, there is consistent risk that further increase of their prevalence might go undetected.

Gepubliceerd: PLoS One 2015;10(1):e0113033
Impact factor: 3.234

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2. Trends in Expanded-Spectrum Cephalosporin-Resistant Escherichia coli and Klebsiella pneumoniae among Dutch Clinical Isolates, from 2008 to 2012
van der Steen M, Leenstra T, Kluytmans JA, van der Bij AK, ISIS-AR study group (inclusief Halaby T)

We investigated time trends in extended-spectrum cephalosporin-resistant Escherichia coli and Klebsiella pneumoniae isolates from different patient settings in The Netherlands from 2008-2012. E. coli and K. pneumoniae isolates from blood and urine samples of patients > = 18 years were selected from the Dutch Infectious Disease Surveillance System-Antimicrobial Resistance (ISIS-AR) database. We used multivariable Poisson regression to study the rate per year of blood stream infections by susceptible and resistant isolates, and generalized estimating equation (GEE) log-binomial regression for trends in the proportion of extended-spectrum cephalosporin-resistant isolates. Susceptibility data of 197,513 E. coli and 38,244 K.

pneumoniae isolates were included. The proportion of extended-spectrum cephalosporin-resistant E. coli and K. pneumoniae isolates from urine and blood samples increased in all patient settings, except for K. pneumoniae isolates from patients admitted to intensive care units. For K. pneumoniae, there was a different time trend between various patient groups ($p<0.01$), with a significantly higher increase in extended-spectrum cephalosporin-resistant isolates from patients attending a general practitioner than in isolates from hospitalized patients. For E. coli, the increasing time trends did not differ among different patient groups. This nationwide study shows a general increase in extended-spectrum cephalosporin-resistant E. coli and K. pneumoniae isolates. However, differences in trends between E. coli en K. pneumoniae underline the importance of E. coli as a community-pathogen and its subsequent influence on hospital resistance level, while for K. pneumoniae the level of resistance within the hospital seems less influenced by the resistance trends in the community.

Gepubliceerd: PLoS One 2015;10(9):e0138088
Impact factor: 3.234

Totale impact factor: 6.458
Gemiddelde impact factor: 3.234

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 3.234
Gemiddelde impact factor: 3.234

Longziekten

1. Adrenomedullin optimises mortality prediction in COPD patients
Brusse-Keizer M, Zuur-Telgen M, van der Palen J, Van der Valk P, Kerstjens H, Boersma W, Blasi F, Kostikas K, Milenkovic B, Tamm M, Stolz D

Background: Current multicomponent scores that predict mortality in COPD patients might underestimate the systemic component of COPD. Therefore, we evaluated the accuracy of circulating levels of proadrenomedullin (MR-proADM) alone or combined with the ADO (Age, Dyspnoea, airflow Obstruction), updated ADO or BOD (Body mass index, airflow Obstruction, Dyspnoea) index to predict all-cause mortality in stable COPD patients.
Methods: This study pooled data of 1285 patients from the COMIC and PROMISE-COPD study.
Results: Patients with high MR-proADM levels (>/=0.87 nmol/l) had a 2.1 fold higher risk of dying than those with lower levels ($p < 0.001$). Based on the C-statistic, the ADOA index (ADO plus MR-proADM) (C = 0.72) was the most accurate predictor followed by the BODA (BOD plus MR-proADM) (C = 0.71) and the updated ADOA index (updated ADO plus MR-proADM) (C = 0.70). Adding MR-proADM to ADO and BOD was superior in forecasting 1- and 2-year mortality. The net percentages of persons with events correctly reclassified (NRI+) within respectively 1-year and 2-year was 31% and 20% for ADO, 31% and 20% for updated ADO and 25% and 19% for BOD. The net percentages of persons without events correctly reclassified (NRI-) within respectively 1-year and 2-year was 26% and 27% for ADO, 27% and 28% for updated ADO and 34% and 34% for BOD.
Conclusions: Adding MR-proADM increased the predictive power of BOD, ADO and updated ADO index.

Gepubliceerd: Respir Med 2015 Mar 6;109(6):734-42
Impact factor: 3.086

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2. Amoxicillin concentrations in relation to beta-lactamase activity in sputum during exacerbations of chronic obstructive pulmonary disease
Brusse-Keizer M, van der Valk PD, van der Zanden RW, Nijdam L, van der Palen J, Hendrix R, Movig K

Background: Acute exacerbations of chronic obstructive pulmonary disease (COPD) are often treated with antibiotics. Theoretically, to be maximally effective, the antibiotic concentration at sites of infection should exceed the minimum inhibitory concentration at which 90% of the growth of potential pathogens is inhibited (MIC90). A previous study showed that most hospitalized COPD patients had sputum amoxicillin concentrations <LMIC90 when treated with amoxicillin/clavulanic acid. Those with adequate sputum concentrations had better clinical outcomes. Low amoxicillin concentrations can be caused by beta-lactamase activity in the lungs. This study investigated whether patients with sputum amoxicillin

concentrations <MIC90 had higher beta-lactamase activity in sputum than patients with a concentration >/=MIC90.
Methods: In total, 23 patients hospitalized for acute exacerbations of COPD and treated with amoxicillin/clavulanic acid were included. Sputum and serum samples were collected at day 3 of treatment to determine beta-lactamase activity in sputum and amoxicillin concentrations in both sputum and serum.
Results: We found no difference in beta-lactamase activity between patients with sputum amoxicillin concentrations <MIC90 and >/=MIC90 (P=0.79). Multivariate logistic regression analysis showed no significant relationship between beta-lactamase activity and sputum amoxicillin concentrations <MIC90 or >/=MIC90 (odds ratio 0.53; 95% confidence interval 0.23-1.2; P=0.13). Amoxicillin concentrations were <MIC90 in 78% of sputum samples and in 30% of serum samples.
Conclusion: In patients treated with amoxicillin/clavulanic acid for an acute exacerbation of COPD, sputum beta-lactamase activity did not differ between those with sputum amoxicillin concentrations <MIC90 or >/=MIC90. The finding that the majority of patients had sputum amoxicillin concentrations <MIC90 suggests that current treatment with antibiotics for acute exacerbations of COPD should be optimized.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis 2015;10:455-61
Impact factor: 3.141

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3. Integration of electronic nose technology with spirometry: validation of a new approach for exhaled breath analysis
de Vries R, Brinkman P, van der Schee MP, Fens N, Dijkers E, Bootsma SK, de Jongh FH, Sterk PJ

New 'omics'-technologies have the potential to better define airway disease in terms of pathophysiological and clinical phenotyping. The integration of electronic nose (eNose) technology with existing diagnostic tests, such as routine spirometry, can bring this technology to 'point-of-care'.We aimed to determine and optimize the technical performance and diagnostic accuracy of exhaled breath analysis linked to routine spirometry.Exhaled breath was collected in triplicate in healthy subjects by an eNose (SpiroNose) based on five identical metal oxide semiconductor sensor arrays (three arrays monitoring exhaled breath and two reference arrays monitoring ambient air) at the rear end of a pneumotachograph. First, the influence of flow, volume, humidity, temperature, environment, etc, was assessed. Secondly, a two-centre case-control study was performed using diagnostic and monitoring visits in day-to-day clinical care in patients with a (differential) diagnosis of asthma, chronic obstructive pulmonary disease (COPD) or lung cancer. Breathprint analysis involved signal processing, environment correction based on alveolar gradients and statistics based on principal component (PC) analysis, followed by discriminant analysis (Matlab2014/SPSS20).Expiratory flow showed a significant linear correlation with raw sensor deflections (R2 = 0.84) in 60 healthy subjects (age 43 +/- 11 years). No correlation was found between sensor readings and exhaled volume, humidity and temperature. Exhaled data after environment correction were highly reproducible for

each sensor array (Cohen's Kappa 0.81-0.94).Thirty-seven asthmatics (41 +/- 14.2 years), 31 COPD patients (66 +/- 8.4 years), 31 lung cancer patients (63 +/- 10.8 years) and 45 healthy controls (41 +/- 12.5 years) entered the cross-sectional study. SpiroNose could adequately distinguish between controls, asthma, COPD and lung cancer patients with cross-validation values ranging between 78-88%.We have developed a standardized way to integrate eNose technology with spirometry. Signal processing techniques and environmental background correction ensured that the multiple sensor arrays within the SpiroNose provided repeatable and interchangeable results. SpiroNose discriminated controls and patients with asthma, COPD and lung cancer with promising accuracy, paving the route towards point-of-care exhaled breath diagnostics.

Gepubliceerd: J Breath Res 2015;9(4):046001
Impact factor: 4.631

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4. Sleep Position Trainer versus Tennis Ball Technique in Positional Obstructive Sleep Apnea Syndrome
Eijsvogel MM, Ubbink R, Dekker J, Oppersma E, de Jongh FH, van der Palen J, Brusse-Keizer MG

Study objective: Positional therapy (PT) is an effective therapy in positional obstructive sleep apnea syndrome (POSAS) when used, but the compliance of PT is low. The objective of this study was to investigate whether a new kind of PT is effective and can improve compliance. Methods: 29 patients were treated with the Sleep Position Trainer (SPT), 26 patients with the Tennis Ball Technique (TBT). At baseline and 1 month polysomnography, Epworth Sleepiness Scale (ESS) and the Quebec Sleep Questionnaire (QSQ) were taken. Daily compliance was objectively measured in both groups. Results: Both therapies prevent supine sleep position to a median of 0% (min-max: SPT 0.0% to 67%, TBT 0.0% to 38.9%), resulting in a treatment success (AHI <5) in 68.0% of the SPT and 42.9% of the TBT patients. The ESS at baseline was <10 in both groups. Sleep quality parameters as wake after sleep onset (WASO; p = 0.001) and awakenings (p = 0.006) improved more in the SPT group. Total QSQ scores (0.4+/-0.2, p = 0.03) and the QSQ domains nocturnal symptoms (0.7+/-0.2, p = 0.01) and social interactions (0.8+/-0.3, p = 0.02) changed in favor of the SPT group. Effective compliance (>/=4 h/night + >/=5 days/week) was 75.9% for the SPT and 42.3% for the TBT users (p = 0.01). Conclusion: In mild POSAS with normal EES the new SPT device and the standard TBT are equally effective in reducing respiratory indices. However, compared to the TBT, sleep quality, quality of life, and compliance improved significantly more in the SPT group.

Gepubliceerd: J Clin Sleep Med 2015;11(2):139-47
Impact factor: 3.053

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5. In vitro study on work of breathing during non-invasive ventilation using a new variable flow generator
Flink RC, van Kaam AH, de Jongh FH

Objective: In an attempt to reduce the work of breathing (WOB) and the risk of respiratory failure, preterm infants are increasingly treated with nasal synchronised biphasic positive airway pressure (BPAP) via the Infant Flow SiPAP system. However, the relatively high resistance of the generator limits the pressure amplitude (PA) and pressure build-up (PB) of this system. This in vitro study investigates the impact of a new generator with improved fluid mechanics on the WOB, PA and PB during BPAP.
Methods: Using a low compliance lung model, WOB, PA and PB, were measured during BPAP using the old and the new Infant Flow generators. Airway resistance (tube sizes 2.5 mm, 3.0 mm and 3.5 mm), nasal interface sizes (small, medium and large) and four different ventilator settings were used to mimic different clinical conditions.
Results: Compared with the old generator, the new generator significantly reduced the WOB between 10% and 70%, depending on the measurement configuration. The maximum PA was higher when using the new (6-7 cm H2O) generator versus the old (3-4 cm H2O) generator. During the first 100 ms of inspiration, the new generator reached between 33% and 40% of the peak pressure compared with 11-20% for the old generator.
Conclusions: This in vitro study shows that a new generator of the Infant Flow SiPAP device results in a significant reduction in WOB and an increase in PA and PB during BPAP. The results of this study need to be confirmed under variable clinical conditions in preterm infants.

Gepubliceerd: Arch Dis Child Fetal Neonatal Ed 2015 Jul;100(4):F327-F331
Impact factor: 3.120

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6. Differences in Adherence to Common Inhaled Medications in COPD
Koehorst-Ter Huurne K, Movig K, van der Valk PD, van der Palen J, Brusse-Keizer M

Objective: To study differences in adherence to common inhaled medications in COPD.
Methods: Adherence of 795 patients was recorded from pharmacy records over 3 years in the COMIC cohort. It was expressed as percentage and deemed good at >/=75-</=125%, sub-optimal >/=50-<75%, and poor <50% (underuse) or >125% (overuse). Most patients used more than one medication, so we present 1379 medication periods.
Results: The percentages of patients with good therapy adherence ranged from 43.2 (beclomethasone) -75.8% (tiotropium); suboptimal from 2.3 (budesonide) -23.3% (fluticasone); underuse from 4.4 (formoterol/budesonide) -18.2% (beclomethasone); and overuse from 5.1 (salmeterol) -38.6% (budesonide). Patients using fluticasone or salmeterol/fluticasone have a 2.3 and 2.0-fold increased risk of suboptimal versus good adherence compared to tiotropium. Patients using salmeterol/fluticasone or beclomethasone have a 2.3- and 4.6-fold increased risk of underuse versus good adherence compared to tiotropium. Patients using budesonide, salmeterol/fluticasone, formoterol/budesonide, ciclesonide and

beclomethasone have an increased risk of overuse versus good adherence compared to tiotropium. Adherence to inhalation medication is inversely related to lung function.
Conclusion: Therapy adherence to inhalation medication for the treatment of COPD is in our study related to the medication prescribed. Tiotropium showed the highest percentage of patients with good adherence, followed by ciclesonide, both dosed once daily. The idea of improving adherence by using combined preparations cannot be confirmed in this study. Further research is needed to investigate the possibilities of improving adherence by changing inhalation medication.

Gepubliceerd: COPD 2015 Mar 16;12(6):643-8
Impact factor: 2.673

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7. Diagnosis of Hemidiaphragmatic Paresis in a Preterm Infant with Transcutaneous Electromyography: A Case Report
Kraaijenga JV, Hutten GJ, de Jongh FH, van Kaam AH

Transcutaneous electromyography of the diaphragm (dEMG) is a noninvasive and easy applicable tool to measure the electrical activity of the diaphragm. dEMG monitoring has recently been introduced in the neonatal intensive care unit as a novel cardiorespiratory monitor providing direct information on diaphragmatic breathing activity. We report a preterm infant with suspected paresis of the right diaphragm measured with transcutaneous dEMG, which showed a clear reduction in the electrical activity of the right-sided diaphragm. In conclusion, dEMG provides valuable information on regional diaphragmatic activity, which can assist the clinician in diagnosing hemidiaphragmatic paresis. (c) 2015 S. Karger AG, Basel.

Gepubliceerd: Neonatology 2015 May 9;108(1):38-41
Impact factor: 2.649

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8. The Effect of Caffeine on Diaphragmatic Activity and Tidal Volume in Preterm Infants
Kraaijenga JV, Hutten GJ, de Jongh FH, van Kaam AH

Objective: To determine the effect of caffeine on diaphragmatic activity, tidal volume (Vt), and end-expiratory lung volume (EELV) in preterm infants.
Study Design: Using transcutaneous electromyography of the diaphragm (dEMG), we measured diaphragmatic activity from 30 minutes before (baseline) to 3 hours after administration of an intravenous caffeine-base loading dose in 30 spontaneously breathing preterm infants (mean gestational age, 29.1 +/- 1.3 weeks), most of whom were on noninvasive respiratory support. Diaphragmatic activity was expressed as the percentage change in dEMG amplitude, area under the curve, respiratory rate, and inspiratory and expiratory times. Using respiratory inductive plethysmography, we measured changes in Vt and EELV from baseline. These outcome variables were calculated at 8 fixed time points after caffeine administration (5, 15, 30, 60, 90, 120, 150, and 180 minutes) and compared with baseline.

Results: Caffeine administration resulted in rapid (within 5 minutes) increases in dEMG amplitude (median, 43%; IQR, 24%-63%; P < .001) and area under the curve (median, 28%; IQR, 14%-48%; P < .001). Vt also increased by a median of 30% (IQR, 7%-48%), and this change was significantly correlated with the change in dEMG amplitude (r = 0.67; P < .001). These effects were relatively stable until 120 minutes after caffeine administration. Caffeine did not consistently impact EELV, respiratory rate, or inspiratory and expiratory times.
Conclusion: Caffeine treatment results in a rapid and sustained increase in diaphragmatic activity and Vt in preterm infants.

Gepubliceerd: J Pediatr 2015 May 15;167(1):70-5
Impact factor: 3.790

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9. Transcutaneous electromyography of the diaphragm: A cardio-respiratory monitor for preterm infants
Kraaijenga JV, Hutten GJ, de Jongh FH, van Kaam AH

Introduction: Chest impedance (CI) is the current standard for cardio-respiratory monitoring in preterm infants but fails to provide direct and quantitative information on diaphragmatic activity. Transcutaneous electromyography (dEMG) is able to measure diaphragmatic activity, but its feasibility and repeatability to monitor respiratory rate (RR) and heart rate (HR) in preterm infants needs to be established.
Methods: RR and HR were measured simultaneously by dEMG and CI for 1-hour on day 1, 3, and 7 of life in 31 preterm infants (gestational age 29.6 +/- 1.8 weeks; birth weight 1380 +/- 350 g) on non-invasive respiratory support. Six fixed 1-minute time intervals were selected from each 1-hour recording and both RR and HR were calculated using all intervals or only those with stable dEMG and CI recordings.
Results: dEMG was well tolerated and signal quality was good. Both RR and HR measured by dEMG and CI were significantly correlated (RR: r = 0.85, HR: r = 0.98) and showed good agreement by the Bland-Altman plot (mean difference (limits of agreement): RR: -2.3 (-17.3 to 12.7) breaths/min and HR: -0.3 (-5.3 to 4.7) beats/min. When analyzing only stable recordings, the correlation (r = 0.92) and agreement (-1.8 (-12.3 to 8.7) breaths/min) for RR improved. Subgroup analyses for postnatal age, gestational age, and mode of support showed similar results suggesting good repeatability of dEMG.
Conclusion: This study shows that monitoring RR and HR with transcutaneous dEMG is feasible and repeatable in preterm infants.

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Impact factor: 2.704

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10. Safety and tolerability of nebulized amoxicillin + clavulanic acid in patients with stable COPD
Nijdam LC, Kuijvenhoven JC, van der Valk PD, Brusse-Keizer MG, van der palen J, Movig KL

Objective: To study the safety and tolerability of nebulized amoxicillin + clavulanic acid in patients with stable copd. Acute exacer- bations in copd are often treated with antibiotics. Previous studies showed ineffective amoxicillin concentrations in sputum in two thirds of the patients treated with systemic amoxicillin + clavulanic acid. Local administration, theo r- etically providing higher concentrations, has not been described before.
Design: Prospective observational intervention study.
Methods: Nine subjects received ascending doses amoxicillin + clavulanic acid, ranging from 50 + 10 mg up to 300 + 60 mg. Plasma and expectorated sputum samples were assayed for amoxicillin content. Safety was evaluated by spirometry before and after nebulization. Tolerability was evaluated by questionnaire.
Results: Spirometry showed no clinically relevant reduction in fev1 after nebulization with amoxicillin + clavulanic acid. In 34 nebulizations only 3 mild adverse events occurred. The sputum amoxicillin quantification showed levels well above mic90, while no effective levels were found in plasma.
Conclusion: Inhalation of nebulized amoxicillin + clavulanic acid is safe and well tolerated. Nebulized amoxicillin + clavulanic acid produces sputum concentrations well above mic with low systemic exposure.

Gepubliceerd: PW Wetenschappelijk Platform. 2015;9:a1510
Impact factor: 0

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11. Changes in Lung Volume and Ventilation Following Transition from Invasive to Non-invasive Respiratory Support and Prone Positioning in Preterm Infants
van der Burg PS, Miedema M, de Jongh FH, Frerichs I, van Kaam AH

Background: To minimize secondary lung injury, ventilated preterm infants are extubated as soon as possible. To maximize extubation success, they are often placed in prone position. The effect of extubation and subsequent prone positioning on lung volumes is currently unknown.
Methods: Changes in end-expiratory lung volume (DeltaEELV), tidal volume (VT) and ventilation distribution were monitored during transition from endotracheal to nasal continuous positive airway pressure and following prone positioning using electrical impedance tomography. In addition, the continuous distending pressure (CDP) and oxygen need (FiO2) were recorded.
Results: 20 preterm infants (GA 28.7+/-1.7 wk) were included. Following extubation the CDP decreased from 7.9+/-0.5 to 6.0+/-0.2 cmH2O, while the FiO2 remained stable. Both DeltaEELV and VT increased significantly ($p<0.05$) after extubation, without changing ventilation distribution. Prone positioning resulted in a further increase in DeltaEELV ($p<0.01$) and a decrease in respiratory rate. VT remained stable but its distribution clearly shifted towards the ventral lung regions.
Conclusion: Infants who are transitioned from invasive to non-invasive respiratory support are able to maintain their EELV and increase their VT. Prone positioning increases EELV and shifts tidal ventilation to the ventral lung regions. The latter suggests that infants should preferably be placed in prone position after extubation.

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Impact factor: 2.314

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12. Protective effect of a low single dose inhaled steroid against exercise induced bronchoconstriction
Visser R, Wind M, de Graaf B, de Jongh FH, van der Palen J, Thio BJ

Objective: Daily use of inhaled corticosteroids (ICS) reduces exercise induced bronchoconstriction (EIB) in asthmatic children. A high single dose of ICS also provided acute protection against EIB. Objective of this study is to investigate whether a low single dose of ICS offers protection against EIB in asthmatic children.
Methods: 31 Mild asthmatic children not currently treated with inhaled corticosteroids, 5-16 years, with EIB (fall in FEV0.5/1 >/= 13%) were included in a prospective intervention study. They performed two ECT's within 2 weeks. Four hours before the second test children inhaled 200 mug beclomethasone-dipropionate (BDP) with a breath-actuated inhaler (BAI).
Results: The median fall in FEV0.5/1 after 200 mug BDP was significantly reduced from 30.9% at baseline to 16.0% (P < 0.001). Twenty children (64.5%) showed a good response to 200 mug BDP (>/=50% decrease in fall of FEV0.5/1), while 8 children showed a moderate response (25-50%), and three children showed no response at all (< 25%).
Conclusion: A low single dose ICS offers acute protection against EIB in the majority of asthmatic children not currently treated with inhaled corticosteroids.

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Impact factor: 2.704

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13. Reversibility after inhaling salbutamol in different body postures in asthmatic children: A pilot study
Visser R, van der Palen J, de Jongh FH, Thio BJ

Rationale: Pulmonary medication is mostly delivered in the form of medical aerosols to minimize systemic side effects. A major drawback of inhaled medication is that the majority of inhaled particles impacts in the oropharynx at the sharp bend of the airway. Stretching the airway by a forward leaning body posture with the neck extended ("sniffing position") may improve pulmonary deposition and clinical effects.
Methods: 41 asthmatic children who were planned for standard reversibility testing at the pulmonary function lab, alternately inhaled 200 mugr salbutamol with an Autohaler((R)) in the standard or in the forward leaning body posture. Forced Expiratory Volume in 1 s (FEV1), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF), Mean Expiratory Flow at 25% of vital capacity (MEF25) and Mean Expiratory Flow at 75% of vital capacity (MEF75) were analysed.
Results: The children in the forward leaning body posture group showed a significantly higher mean FEV1 reversibility than the control group after inhalation of 200 mugr salbutamol (10.2% versus 4.1%, p = 0.019). Additionally, mean MEF75

was significantly more reversible in the forward leaning body posture group versus the standard body posture group (32.2% resp. 8.9%, p = 0.013).
Conclusion: This pilot study showed a higher reversibility of FEV1 and MEF75 after inhaling salbutamol in a forward leaning body posture compared to the standard body posture in asthmatic children. This suggests that pulmonary effects of salbutamol can be improved by inhaling in a forward leaning body posture with the neck extended. This effect is possibly due to a higher pulmonary deposition of salbutamol and should be confirmed in a randomized controlled trial.

Gepubliceerd: Respir Med 2015 Apr;109(4):459-62
Impact factor: 3.086

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14. Reversibility of pulmonary function after inhaling salbutamol in different doses and body postures in asthmatic children
Visser R, Kelderman S, de Jongh FH, van der Palen J, Thio BJ

Rationale: Pulmonary medication is often delivered in the form of medical aerosols designed for inhalation. Recently, breath actuated inhalers (BAI's) gained popularity as they can be used without spacers. A major drawback of BAI's is the impaction in the upper airway. Stretching the upper airway by a forward leaning body posture with the neck extended ("sniffing position") during inhalation may reduce upper airway impaction and improve pulmonary deposition. Aim of this study was to investigate the reversibility of lung function with different doses salbutamol inhaled with a BAI in the forward leaning posture compared to the standard posture in asthmatic children.
Methods: 22 clinically stable asthmatic children, 5-14 years old, performed four reversibility measurements. Children inhaled 200 mug or 400 mug salbutamol with a BAI in the standard or in the forward leaning posture with the neck extended in a randomized single-blinded cross-over design.
Results: Reversibility of lung function after inhaling salbutamol in the forward leaning posture was not significantly different compared to inhalation in the standard posture. Mean FEV1 reversibility was significantly greater after inhaling 400 mug salbutamol compared to 200 mug salbutamol in the standard posture (9.4% +/- 9.5% versus 4.5% +/- 7.5%, difference 4.9% (95CI 0.9; 9.0%); p = 0.021).
Conclusion: In clinically stable asthmatic children, inhalation of salbutamol with a BAI in a forward leaning posture does not increase reversibility of lung function. Inhalation of 400 mug compared to 200 mug salbutamol with a BAI does improve reversibility.

Gepubliceerd: Respir Med 2015 Jul 23;109(10):1274-9
Impact factor: 3.086

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15. The effect of body posture during medication inhalation on exercise induced bronchoconstriction in asthmatic children
Visser R, Wind M, de Graaf BJ, de Jongh FH, van der Palen J, Thio BJ

Rationale: Inhaling medication in a standard body posture leads to impaction of particles in the sharp angle of the upper airway. Stretching the upper airway by extending the neck in a forward leaning body posture may improve pulmonary deposition. A single dose of inhaled corticosteroids (ICS) offers acute, but moderate protection against exercise induced bronchoconstriction (EIB). This study investigated whether inhaling a single dose of ICS in a forward leaning posture improves this protection against EIB.
Methods: 32 Asthmatic children, 5-16 years, with EIB (Median fall in FEV1 or FEV0.5 30.9%) performed two exercise challenge tests (ECT's) with spirometry in a single blinded cross-over trial design. Children inhaled a single dose of 200 mug beclomethasone dipropionate (BDP) 4 h before the ECT, once in the standard posture and once with the neck extended in a forward leaning posture. Spirometry was also performed before the inhalation of the single dose of BDP.
Results: Inhalation of BDP in both body postures provided similar protection against EIB (fall in FEV1 or FEV0.1 in standard posture 16.7%; in forward leaning posture 15.1%, p = 0.83). Inhaling ICS in a forward leaning posture significantly delayed EIB compared to inhaling in the standard posture (respectively 2.5 min +/- 1.0 min vs. 1.6 min +/- 0.8 min; difference 0.9 min (95CI 0.25; 1.44 min); p = 0.01).
Conclusion: Inhalation of a single dose BDP in both the forward leaning posture and the standard posture provided effective and similar protection against EIB in asthmatic children, but the forward leaning posture resulted in a delay of EIB.
Register: NTR3432 (www.trialregister.nl).

Respir Med 2015 Oct;109(10):1257-61
Impact factor: 3.086

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16. Cost-Effectiveness of a Community-Based Exercise Programme in COPD Self-Management
Zwerink M, Effing T, Kerstjens HA, van der Valk PD, Brusse-Keizer M, Zielhuis G, van der Palen J

Introduction: Information regarding cost-effectiveness of community-based exercise programmes in COPD is scarce. Therefore, we have investigated whether a community-based exercise programme is a cost-effective component of self-management for patients with COPD after 2 years of follow-up.
Methods: All included COPD patients participated in four self-management sessions. Additionally, patients in the COPE-active group participated in an 11-month community-based exercise programme led by physiotherapists. Patients trained 3 times/week for 6 months and two times/week during the subsequent 5 months. In both periods, one of these weekly training sessions was home-based (unsupervised). No formal physiotherapy sessions were offered to COPE-active patients in the second year. A decision analytical model with a 24-month perspective was used to evaluate cost-effectiveness. Incremental cost-effectiveness ratios (ICER) were calculated and cost-effectiveness planes were created.
Results: Data of 77 patients participating in the exercise programme and 76 patients in the control group were analysed. The ICER for an additional patient prevented from deteriorating at least 47.5 meters on the ISWT was euro6257. The

ICER for an additional patient with a clinically relevant improvement (>/= 500 steps/day) in physical activity was euro1564, and the ICER for an additional quality-adjusted life year (QALY) was euro10 950.
Conclusion: Due to a lack of maintenance of beneficial effects on our primary outcome exercise capacity after 2 years of follow-up and higher costs of the programme, the community-based exercise programme cannot be considered cost-effective compared to self-management programmes only. Nevertheless, the ICERs for the secondary outcomes physical activity and QALY are generally considered acceptable.

Gepubliceerd: COPD 2015 Dec 1;1-10
Impact factor: 2.673

Totale impact factor: 45.796
Gemiddelde impact factor: 2.862

Aantal artikelen 1e, 2e of laatste auteur: 7
Totale impact factor: 17.746
Gemiddelde impact factor: 2.535

MDL

1. Identification of Patients With Variants in TPMT and Dose Reduction Reduces Hematologic Events During Thiopurine Treatment of Inflammatory Bowel Disease

Coenen MJ, de Jong DJ, van Marrewijk CJ, Derijks LJ, Vermeulen SH, Wong DR, Klungel OH, Verbeek AL, Hooymans PM, Peters WH, te Morsche RH, Newman WG, Scheffer H, Guchelaar HJ, Franke B, TOPIC Recruitment Team, includes Kolkman JJ

Background & aims: More than 20% of patients with inflammatory bowel disease (IBD) discontinue thiopurine therapy because of severe adverse drug reactions (ADRs); leukopenia is one of the most serious ADRs. Variants in the gene encoding thiopurine S-methyltransferase (TPMT) alter its enzymatic activity, resulting in higher levels of thiopurine metabolites, which can cause leukopenia. We performed a prospective study to determine whether genotype analysis of TPMT before thiopurine treatment, and dose selection based on the results, affects the outcomes of patients with IBD.
Methods: In a study performed at 30 Dutch hospitals, patients were assigned randomly to groups that received standard treatment (control) or pretreatment screening (intervention) for 3 common variants of TPMT (TPMT*2, TPMT*3A, and TPMT*3C). Patients in the intervention group found to be heterozygous carriers of a variant received 50% of the standard dose of thiopurine (azathioprine or 6-mercaptopurine), and patients homozygous for a variant received 0%-10% of the standard dose. We compared, in an intention-to-treat analysis, outcomes of the intervention (n = 405) and control groups (n = 378) after 20 weeks of treatment. Primary outcomes were the occurrence of hematologic ADRs (leukocyte count < 3.0*10(9)/L or reduced platelet count < 100*10(9)/L) and disease activity (based on the Harvey-Bradshaw Index for Crohn's disease [n = 356] or the partial Mayo score for ulcerative colitis [n = 253]).
Results: Similar proportions of patients in the intervention and control groups developed a hematologic ADR (7.4% vs 7.9%; relative risk, 0.93; 95% confidence interval, 0.57-1.52) in the 20 weeks of follow-up evaluation; the groups also had similar mean levels of disease activity (P = .18 for Crohn's disease and P = .14 for ulcerative colitis). However, a significantly smaller proportion of carriers of the TPMT variants in the intervention group (2.6%) developed hematologic ADRs compared with patients in the control group (22.9%) (relative risk, 0.11; 95% confidence interval, 0.01-0.85).
Conclusions: Screening for variants in TPMT did not reduce the proportions of patients with hematologic ADRs during thiopurine treatment for IBD. However, there was a 10-fold reduction in hematologic ADRs among variant carriers who were identified and received a dose reduction, compared with variant carriers who did not, without differences in treatment efficacy. ClinicalTrials.gov number: NCT00521950.

Gastroenterology 2015 Oct;149(4):907-17
Impact factor: 16.716

2. Surveillance in patients with long-segment Barrett's oesophagus: a cost-effectiveness analysis
Kastelein F, van Olphen S, Steyerberg EW, Sikkema M, Spaander MC, Looman CW, Kuipers EJ, Siersema PD, Bruno MJ, de Bekker-Grob EW, ProBar-study group, includes Kolkman JJ

Objective: Surveillance is recommended for Barrett's oesophagus (BO) to detect early oesophageal adenocarcinoma (OAC). The aim of this study was to evaluate the cost-effectiveness of surveillance.
Design: We included 714 patients with long-segment BO in a multicentre prospective cohort study and used a multistate Markov model to calculate progression rates from no dysplasia (ND) to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and OAC. Progression rates were incorporated in a decision-analytic model, including costs and quality of life data. We evaluated different surveillance intervals for ND and LGD, endoscopic mucosal resection (EMR), radiofrequency ablation (RFA) and oesophagectomy for HGD or early OAC and oesophagectomy for advanced OAC. The incremental cost-effectiveness ratio (ICER) was calculated in costs per quality-adjusted life-year (QALY).
Results: The annual progression rate was 2% for ND to LGD, 4% for LGD to HGD or early OAC and 25% for HGD or early OAC to advanced OAC. Surveillance every 5 or 4 years with RFA for HGD or early OAC and oesophagectomy for advanced OAC had ICERs of euro5.283 and euro62.619 per QALY for ND. Surveillance every five to one year had ICERs of euro4.922, euro30.067, euro32.531, euro41.499 and euro75.601 per QALY for LGD. EMR prior to RFA was slightly more expensive, but important for tumour staging.
Conclusions: Based on a Dutch healthcare perspective and assuming a willingness-to-pay threshold of euro35.000 per QALY, surveillance with EMR and RFA for HGD or early OAC, and oesophagectomy for advanced OAC is cost-effective every 5 years for ND and every 3 years for LGD.

Gut 2015 Jun;64(6):864-71
Impact factor: 14.660

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3. Use of Visible Light Spectroscopy to Diagnose Chronic Gastrointestinal Ischemia and Predict Response to Treatment
Sana A, Moons LM, Hansen BE, Dewint P, van Noord D, Mensink PB, Kuipers EJ

Background & Aims: Chronic gastrointestinal ischemia (CGI) is more common than previously thought. Visible light spectroscopy (VLS) allows for noninvasive measurements of mucosal capillary hemoglobin oxygen saturation during endoscopy. We evaluated the response of patients with occlusive CGI to treatment after evaluation by radiologic imaging of the vasculature and VLS. We also identified factors associated with response to treatment in these patients.
Methods: In a prospective study, we collected data from 212 patients referred for evaluation of suspected CGI from November 2008 through January 2011. Patients underwent an extensive evaluation that included visualization of gastrointestinal

arteries and assessments of mucosal perfusion by means of VLS. Treatment response was evaluated in patients with occlusive CGI. Factors associated with response to therapy were assessed by using multivariate logistic regression analysis.
Results: Occlusive CGI was diagnosed in 107 patients (50%); 96 were offered treatment (90%). After median follow-up period of 13 months, data on treatment response were available from 89 patients (93%); 62 patients had a sustained response (70%). Weight loss before treatment (odds ratio [OR], 1.93), presence of an abdominal bruit (OR, 2.36), and corpus mucosal saturation level <56% (OR, 4.84) were the strongest predictors of a positive response to treatment.
Conclusions: Treatment of CGI, diagnosed by a multimodal approach, provides a substantial long-term rate of response (70% in 13 months). Weight loss, abdominal bruit, and low corpus mucosal saturation identify patients most likely to respond to treatment. Multiple techniques should therefore be used to assess patients with CGI, including VLS measurements, to detect mucosal hypoxia.

Gepubliceerd: Clin Gastroenterol Hepatol 2015 Jul 11;13(1):122-30
Impact factor: 7.896

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4. HLA-DRB1*03:01 and HLA-DRB1*04:01 modify the presentation and outcome in autoimmune hepatitis type-1
van Gerven NM, de Boer YS, Zwiers A, Verwer BJ, Drenth JP, van Hoek B, van Erpecum KJ, Beuers U, van Buuren HR, den Ouden JW, Verdonk RC, Koek GH, Brouwer JT, Guichelaar MM, Vrolijk JM, Coenraad MJ, Kraal G, Mulder CJ, van Nieuwkerk CM, Bloemena E, Verspaget HW, Kumar V, Zhernakova A, Wijmenga C, Franke L, Bouma G

The classical human leukocyte antigen (HLA)-DRB1*03:01 and HLA-DRB1*04:01 alleles are established autoimmune hepatitis (AIH) risk alleles. To study the immune-modifying effect of these alleles, we imputed the genotypes from genome-wide association data in 649 Dutch AIH type-1 patients. We therefore compared the international AIH group (IAIHG) diagnostic scores as well as the underlying clinical characteristics between patients positive and negative for these HLA alleles. Seventy-five percent of the AIH patients were HLA-DRB1*03:01/HLA-DRB1*04:01 positive. HLA-DRB1*03:01/HLA-DRB1*04:01-positive patients had a higher median IAIHG score than HLA-DRB1*03:01/HLA-DRB1*04:01-negative patients (P<0.001). We did not observe associations between HLA alleles and alanine transaminase levels (HLA-DRB1*03:01: P=0.2; HLA-DRB1*04:01; P=0.5); however, HLA-DRB1*03:01 was independently associated with higher immunoglobulin G levels (P=0.04). The HLA-DRB1*04:01 allele was independently associated with presentation at older age (P=0.03) and a female predominance (P=0.04). HLA-DRB1*03:01-positive patients received immunosuppressive medication and liver transplantation. In conclusion, the HLA-DRB1*03:01 and HLA-DRB1*04:01 alleles are both independently associated with the aggregate diagnostic IAIHG score in type-1 AIH patients, but are not essential for AIH development. HLA-DRB1*03:01 is the strongest genetic modifier of disease severity in AIH.

Gepubliceerd: Genes Immun 2015 Jun;16(4):247-52
Impact factor: 2.913

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5. Cost Efficacy of Metal Stents for Palliation of Extrahepatic Bile Duct Obstruction in a Randomized Controlled Trial
Walter D, van Boeckel PG, Groenen MJ, Weusten BL, Witteman BJ, Tan G, Brink MA, Nicolai J, Tan AC, Alderliesten J, Venneman NG, Laleman W, Jansen JM, Bodelier A, Wolters FL, van der Waaij LA, Breumelhof R, Peters FT, Scheffer RC, Leenders M, Hirdes MM, Steyerberg EW, Vleggaar FP, Siersema PD

Background & Aims: Endoscopic stents are placed for palliation of extrahepatic bile duct obstruction. Although self-expandable metal stents (SEMS) remain patent longer than plastic stents, they are more expensive. We aimed to evaluate which type of stent (plastic, uncovered SEMS [uSEMS], or partially covered SEMS [pcSEMS]) is the most effective and we assessed costs.
Methods: We performed a multicenter randomized trial in 219 patients at 18 hospitals in The Netherlands from February 2008 through February 2013. Patients were assigned randomly for placement of a plastic stent (n = 73), uSEMS (n = 75), or pcSEMS (n = 71) during endoscopic retrograde cholangiopancreatography. Patients were followed up for up to 1 year. Researchers were not blinded to groups. The main study end points included functional stent time and costs.
Results: The mean functional stent times were 172 days for plastic stents, 288 days for uSEMS, and 299 days for pcSEMS (P < .005 for uSEMS and pcSEMS vs plastic). The initial placement of plastic stents (euro1042 or $1106) cost significantly less than placement of SEMS (euro1973 or $2094) (P = .001). However, the total cost per patient at the end of the follow-up period did not differ significantly between plastic stents (euro7320 or $7770) and SEMS (euro6932 or $7356) (P = .61). Furthermore, in patients with short survival times (</=3 mo) or metastatic disease, the total cost per patient did not differ between plastic stents and SEMS. No differences in costs were found between pcSEMS and uSEMS.
Conclusions: Although placement of SEMS (uncovered or partially covered) for palliation of extrahepatic bile duct obstruction initially is more expensive than placement of plastic stents, SEMS have longer functional time. The total costs after 1 year do not differ significantly with stent type.
Dutch Clinical Trial Registration no: NTR1361.

Gepubliceerd: Gastroenterology 2015 Jul;149(1):130-8
Impact factor: 16.716

Totale impact factor: 58.901
Gemiddelde impact factor: 11.780

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

Medical School Twente

1. Rapid enzyme analysis as a diagnostic tool for wound infection: Comparison between clinical judgment, microbiological analysis and enzyme analysis
Blokhuis-Arkes MH, Haalboom M, van der Palen J, Heinzle A, Sigl E, Guebitz G, Beuk R

In clinical practice, diagnosis of wound infection is based on the classical clinical signs of infection. When infection is suspected, wounds are often swabbed for microbiological culturing. These methods are not accurate (clinical judgment in chronic wounds) or provide results after several days (wound swab). Therefore, there is an urgent need for an easy-to-use diagnostic tool for fast detection of wound infection, especially in chronic wounds. This study determined the diagnostic properties of the enzymes myeloperoxidase (MPO), human neutrophil elastase (HNE), lysozyme and cathepsin-G in detecting wound infection when compared to wound swabs. Both chronic and acute wounds of 81 patients were assessed through clinical judgment, enzyme analysis and wound swab. Three promising enzyme models for detecting wound infection were identified. A positive test was defined as: at least one enzyme positive after 30 minutes (model 1), lysozyme and HNE positive after 30 minutes (model 2), MPO positive after 5 minutes, and HNE or lysozyme positive after 30 minutes (model 3). All models were significant (p</=0.001). There was no correlation between clinical judgment and wound swab, indicating the need for novel diagnostic systems. Enzyme analysis is fast, easy to use and superior to clinical judgment when compared to wound swabs.

Gepubliceerd: Wound Repair Regen 2015 Mar 26;23(3):345-52
Impact factor: 2.745

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2. Adrenomedullin optimises mortality prediction in COPD patients
Brusse-Keizer M, Zuur-Telgen M, van der Palen J, Van der Valk P, Kerstjens H, Boersma W, Blasi F, Kostikas K, Milenkovic B, Tamm M, Stolz D

Background: Current multicomponent scores that predict mortality in COPD patients might underestimate the systemic component of COPD. Therefore, we evaluated the accuracy of circulating levels of proadrenomedullin (MR-proADM) alone or combined with the ADO (Age, Dyspnoea, airflow Obstruction), updated ADO or BOD (Body mass index, airflow Obstruction, Dyspnoea) index to predict all-cause mortality in stable COPD patients.
Methods: This study pooled data of 1285 patients from the COMIC and PROMISE-COPD study.
Results: Patients with high MR-proADM levels (>/=0.87 nmol/l) had a 2.1 fold higher risk of dying than those with lower levels (p < 0.001). Based on the C-statistic, the ADOA index (ADO plus MR-proADM) (C = 0.72) was the most accurate predictor followed by the BODA (BOD plus MR-proADM) (C = 0.71) and the updated ADOA index (updated ADO plus MR-proADM) (C = 0.70). Adding MR-proADM to ADO and

BOD was superior in forecasting 1- and 2-year mortality. The net percentages of persons with events correctly reclassified (NRI+) within respectively 1-year and 2-year was 31% and 20% for ADO, 31% and 20% for updated ADO and 25% and 19% for BOD. The net percentages of persons without events correctly reclassified (NRI-) within respectively 1-year and 2-year was 26% and 27% for ADO, 27% and 28% for updated ADO and 34% and 34% for BOD.
Conclusions: Adding MR-proADM increased the predictive power of BOD, ADO and updated ADO index.

Gepubliceerd: Respir Med 2015 Mar 6;109(6):734-42
Impact factor: 3.086

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3. Amoxicillin concentrations in relation to beta-lactamase activity in sputum during exacerbations of chronic obstructive pulmonary disease
Brusse-Keizer M, van der Valk PD, van der Zanden RW, Nijdam L, van der Palen J, Hendrix R, Movig K

Background: Acute exacerbations of chronic obstructive pulmonary disease (COPD) are often treated with antibiotics. Theoretically, to be maximally effective, the antibiotic concentration at sites of infection should exceed the minimum inhibitory concentration at which 90% of the growth of potential pathogens is inhibited (MIC90). A previous study showed that most hospitalized COPD patients had sputum amoxicillin concentrations <LMIC90 when treated with amoxicillin/clavulanic acid. Those with adequate sputum concentrations had better clinical outcomes. Low amoxicillin concentrations can be caused by beta-lactamase activity in the lungs. This study investigated whether patients with sputum amoxicillin concentrations <MIC90 had higher beta-lactamase activity in sputum than patients with a concentration >/=MIC90.
Methods: In total, 23 patients hospitalized for acute exacerbations of COPD and treated with amoxicillin/clavulanic acid were included. Sputum and serum samples were collected at day 3 of treatment to determine beta-lactamase activity in sputum and amoxicillin concentrations in both sputum and serum.
Results: We found no difference in beta-lactamase activity between patients with sputum amoxicillin concentrations <MIC90 and >/=MIC90 (P=0.79). Multivariate logistic regression analysis showed no significant relationship between beta-lactamase activity and sputum amoxicillin concentrations <MIC90 or >/=MIC90 (odds ratio 0.53; 95% confidence interval 0.23-1.2; P=0.13). Amoxicillin concentrations were <MIC90 in 78% of sputum samples and in 30% of serum samples.
Conclusion: In patients treated with amoxicillin/clavulanic acid for an acute exacerbation of COPD, sputum beta-lactamase activity did not differ between those with sputum amoxicillin concentrations <MIC90 or >/=MIC90. The finding that the majority of patients had sputum amoxicillin concentrations <MIC90 suggests that current treatment with antibiotics for acute exacerbations of COPD should be optimized.

Gepubliceerd: Int J Chron Obstruct Pulmon Dis 2015;10:455-61

Impact factor: 3.141

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4. Use of Calscan for improving osteoporosis care in the older patient admitted with hip fracture
De Klerk G, Hegeman JH, van der Palen J, Ten Duis HJ

To determine whether bone mineral density measurement using the Calscan successfully predicts the actual bone mineral density, as measured by dual-energy X-ray absorptiometry. We included all patients >/= 65 years with a hip fracture screened on osteoporosis by both dual-energy X-ray absorptiometry and the Calscan during the period April 2008 to April 2011. The bone mineral density was expressed as a T-score. For the Calscan T-score, thresholds were defined such that patients with and without osteoporosis could be identified with 90% certainty. Patients with a Calscan T-score above the upper threshold were considered to be non-osteoporotic and those with a Calscan T-score below the lower threshold considered osteoporotic. Patients whose Calscan T-score lay between the two thresholds could only be classified by means of DXA. The correlation between dual-energy X-ray absorptiometry and the Calscan was 0.61. The Calscan identified approximately 25% of patients as osteoporotic and 25% as non-osteoporotic. The upper threshold was found to be -1.8SD and the lower threshold -3.5SD. Osteoporosis screening by dual-energy X-ray absorptiometry had been carried out in 44% of patients. This percentage could theoretically rise to > 70% if the Calscan is implemented in osteoporosis screening, while costs of such screening appear to be lower, as long as a sufficient number of patients are screened.

Gepubliceerd: Acta Orthop Belg 2015 Mar;81(1):23-9
Impact factor: 0.654

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5. Automatic day-2 intervention by a multidisciplinary antimicrobial stewardship-team leads to multiple positive effects
Dik JW, Hendrix R, Lo-Ten-Foe JR, Wilting KR, Panday PN, van Gemert-Pijnen LE, Leliveld AM, van der Palen J, Friedrich AW, Sinha B

Background: Antimicrobial resistance rates are increasing. This is, among others, caused by incorrect or inappropriate use of antimicrobials. To target this, a multidisciplinary antimicrobial stewardship-team (A-Team) was implemented at the University Medical Center Groningen on a urology ward. Goal of this study is to evaluate the clinical effects of the case-audits done by this team, looking at length of stay (LOS) and antimicrobial use.
Methods: Automatic e-mail alerts were sent after 48 h of consecutive antimicrobial use triggering the case-audits, consisting of an A-Team member visiting the ward, discussing the patient's therapy with the bed-side physician and together deciding on further treatment based on available diagnostics and guidelines. Clinical effects of the audits were evaluated through an Interrupted Time Series analysis and a retrospective historic cohort.

Results: A significant systemic reduction of antimicrobial consumption for all patients on the ward, both with and without case-audits was observed. Furthermore, LOS for patients with case-audits who were admitted primarily due to infections decreased to 6.20 days (95% CI: 5.59-6.81) compared to the historic cohort (7.57 days; 95% CI: 6.92-8.21; p = 0.012). Antimicrobial consumption decreased for these patients from 8.17 DDD/patient (95% CI: 7.10-9.24) to 5.93 DDD/patient (95% CI: 5.02-6.83; p = 0.008). For patients with severe underlying diseases (e.g., cancer) these outcome measures remained unchanged.
Conclusion: The evaluation showed a considerable positive impact. Antibiotic use of the whole ward was reduced, transcending the intervened patients. Furthermore, LOS and mean antimicrobial consumption for a subgroup was reduced, thereby improving patient care and potentially lowering resistance rates.

Gepubliceerd: Front Microbiol 2015;6:546
Impact factor: 3.989

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6. Sleep Position Trainer versus Tennis Ball Technique in Positional Obstructive Sleep Apnea Syndrome
Eijsvogel MM, Ubbink R, Dekker J, Oppersma E, de Jongh FH, van der Palen J, Brusse-Keizer MG

Study objective: Positional therapy (PT) is an effective therapy in positional obstructive sleep apnea syndrome (POSAS) when used, but the compliance of PT is low. The objective of this study was to investigate whether a new kind of PT is effective and can improve compliance.
Methods: 29 patients were treated with the Sleep Position Trainer (SPT), 26 patients with the Tennis Ball Technique (TBT). At baseline and 1 month polysomnography, Epworth Sleepiness Scale (ESS) and the Quebec Sleep Questionnaire (QSQ) were taken. Daily compliance was objectively measured in both groups.
Results: Both therapies prevent supine sleep position to a median of 0% (min-max: SPT 0.0% to 67%, TBT 0.0% to 38.9%), resulting in a treatment success (AHI <5) in 68.0% of the SPT and 42.9% of the TBT patients. The ESS at baseline was <10 in both groups. Sleep quality parameters as wake after sleep onset (WASO; p = 0.001) and awakenings (p = 0.006) improved more in the SPT group. Total QSQ scores (0.4+/-0.2, p = 0.03) and the QSQ domains nocturnal symptoms (0.7+/-0.2, p = 0.01) and social interactions (0.8+/-0.3, p = 0.02) changed in favor of the SPT group. Effective compliance (>/=4 h/night + >/=5 days/week) was 75.9% for the SPT and 42.3% for the TBT users (p = 0.01).
Conclusion: In mild POSAS with normal EES the new SPT device and the standard TBT are equally effective in reducing respiratory indices. However, compared to the TBT, sleep quality, quality of life, and compliance improved significantly more in the SPT group.

Gepubliceerd: J Clin Sleep Med 2015;11(2):139-47
Impact factor: 3.053

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7. Long Term Results of Kissing Stents in the Aortic Bifurcation
Hinnen JW, Konickx MA, Meerwaldt R, Kolkert JL, van der Palen J, Huisman AB, Geelkerken RH

Background: To evaluate the long-term outcome after aortoiliac kissing stent placement and to analyze variables, which potentially influence the outcome of endovascular reconstruction of the aortic bifurcation.
Methods: All patients treated with aortoiliac kissing stents at our institution between April 1995 and August 2011 were retrospectively identified from a prospective single-center database. Data regarding patient characteristics (age, gender, smoking, cardio- and cerebrovascular risk factors, hyperlipidaemia, diabetes mellitus and use of antihypertensive medication), symptoms, pre-interventional examination and imaging, procedural details and follow-up were retrieved. Patency rates were calculated with Kaplan-Meier analysis. Factors affecting the patency were determined with Cox uni- and multivariate analysis.
Results: A total of 215 patients (63% men, mean age 61 +/- 10 years) were included. The median follow-up period was 31 (IQR 47.1) months. Primary, primary assisted, and secondary patency rates were 97%, 97%, and 99%, respectively, at one month; 92%, 95% and 94% at four months; 75%, 86%, and 91% at two years; 70%, 81%, and 91% at 5 years; and 67%, 81%, and 91% at ten years. Younger age and previous aortoiliac treatment were predictors for reduced primary and primary assisted patency. Smoking, previous aortoiliac intervention, TASC C and D lesions were predictors for reduced secondary patency.
Conclusions: Reconstruction of the aortoiliac bifurcation with kissing stents is feasible, safe and effective in all types of lesions with satisfying long term patencies. TASC C and D lesions are associated with a higher occlusion rate. Younger age and previous aortoiliac interventions are predictors for reduced primary and primary assisted patency.

Gepubliceerd: Acta Chir Belg 2015 May;115(3):191-7
Impact factor: 0.408

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8. Bilateral breast cancer, synchronous and metachronous; differences and outcome
Jobsen JJ, van der Palen J, Ong F, Riemersma S, Struikmans H

The aims of this study were twofold: to analyze the incidence of patients having synchronous or metachronous bilateral invasive breast cancer (SBBC and MBBC) and to assess the characteristics and outcome compared to those having unilateral breast cancer (UBC). The used data were obtained from our prospective population-based cohort study which had been started in 1983. Bilateral breast cancer (BBC) was categorized as SBBC (</=3 months of the first primary) or MBBC (>3 months after the first primary). The incidence of SBBC was 1 % and that of MBBC 7.0 %. Patients with UBC showed more ductal carcinoma compared to patients with BBC. MBBC status was an independent significant predictor of local failure (HR 1.9; 95 % CI 1.3-2.7). SBBC status was an independent predictor of distant metastases (HR

2.6; 95 % CI 1.4-4.5). Overall survival (OS) was better for MBBC (HR 0.6; 95 % CI 0.4-0.8) and worse for SBBC (HR 2.3; 95 % CI 1.5-3.6) compared to UBC. We noted: (1) MBBC showed a significant higher local failure compared to UBC, (2) SBBC, compared to MBBC and UBC had a significant higher distant metastases rate, (3) disease-specific survival and OS were significantly worse for SBBC compared to UBC and MBBC, and (4) that the OS for MBBC compared to UBC, was significantly better.

Gepubliceerd: Breast Cancer Res Treat 2015 Sep;153(2):277-83
Impact factor: 3.940

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9. Long-term effects of first degree family history of breast cancer in young women: Recurrences and bilateral breast cancer
Jobsen JJ, van der Palen J, Brinkhuis M, Ong F, Struikmans H

Background: The aim of this study is to analyze the impact of first degree relative (FDR) of young breast cancer patients.
Methods: Data were used from our prospective population-based cohort study which started in 1983. The family history (FH) was registered with regard to FDR: the presence or absence of invasive breast cancer in none vs. one or more FDRs at any age.
Results: A total of 1109 women, </=50 years with 1128 breast conserving treatments was seen. The incidence of FDR was 17.0% for one FDR and 3.2% >/=2 FDR. The three groups, none, 1 or >/=2 FDR, were comparable. The local failure rate is comparable for all three groups. Women with a positive FH and metachronous bilateral breast cancer (MBBC) showed a lower local failure (HR 0.2; 95% CI 0.05-0.8). A positive FH was an independent predictor for a better disease-specific survival (HR 0.6; 95% CI 0.4-0.9).
Conclusion: A positive FH, based on FDR implies a better prognosis in relation to survival for young women treated with BCT. In contrast to no FH for FDR, MBBC in women with a positive FH was not associated with an increased risk of local recurrence.

Gepubliceerd: Acta Oncol 2015 Sep 23;1-6
Impact factor: 2.997

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10. The prognostic relevance of the mitotic activity index in axillary lymph node-negative breast cancer
Jobsen JJ, van der Palen J, Brinkhuis M, Nortier JW, Struikmans H

The aim of the present study is to look at the mitotic activity index (MAI) as a prognostic factor in a prospective population-based cohort of lymph node-negative invasive breast cancer patients. Analyses were based on 2,048 breast-conserving therapies in 1,971 patients, node-negative, and without any form of adjuvant systemic therapy with long-term follow-up. The 15-year distant metastases-free survival (DMFS) for women </=55 years was 88.3 % for low MAI values (</=12)

versus 73.4 % for high MAI values (>12); (HR 2.8; 95 % CI 1.8-4.4; p < 0.001). Multivariate analyses for DMFS showed significance for MAI. For MAI and Bloom-Richardson grading, by performing a likelihood ratio test, we showed the statistical significance for both. For women >55-years, the MAI was not an independent significant factor. We also confirmed the above findings for disease-specific survival. When multi-gene assays are not available, the MAI remains a robust prognostic marker in women younger than 55 years of age with early node-negative breast cancer.

Gepubliceerd: Breast Cancer Res Treat 2015;149(2):343-51
Impact factor: 3.940

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11. Differences in Adherence to Common Inhaled Medications in COPD
Koehorst-Ter Huurne K, Movig K, van der Valk PD, van der Palen J, Brusse-Keizer M

Objective: To study differences in adherence to common inhaled medications in COPD.
Methods: Adherence of 795 patients was recorded from pharmacy records over 3 years in the COMIC cohort. It was expressed as percentage and deemed good at >/=75-</=125%, sub-optimal >/=50-<75%, and poor <50% (underuse) or >125% (overuse). Most patients used more than one medication, so we present 1379 medication periods.
Results: The percentages of patients with good therapy adherence ranged from 43.2 (beclomethasone) -75.8% (tiotropium); suboptimal from 2.3 (budesonide) -23.3% (fluticasone); underuse from 4.4 (formoterol/budesonide) -18.2% (beclomethasone); and overuse from 5.1 (salmeterol) -38.6% (budesonide). Patients using fluticasone or salmeterol/fluticasone have a 2.3 and 2.0-fold increased risk of suboptimal versus good adherence compared to tiotropium. Patients using salmeterol/fluticasone or beclomethasone have a 2.3- and 4.6-fold increased risk of underuse versus good adherence compared to tiotropium. Patients using budesonide, salmeterol/fluticasone, formoterol/budesonide, ciclesonide and beclomethasone have an increased risk of overuse versus good adherence compared to tiotropium. Adherence to inhalation medication is inversely related to lung function.
Conclusion: Therapy adherence to inhalation medication for the treatment of COPD is in our study related to the medication prescribed. Tiotropium showed the highest percentage of patients with good adherence, followed by ciclesonide, both dosed once daily. The idea of improving adherence by using combined preparations cannot be confirmed in this study. Further research is needed to investigate the possibilities of improving adherence by changing inhalation medication.

Gepubliceerd: COPD 2015 Mar 16;12(6):643-8
Impact factor: 2.673

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12. Coronary artery dominance and the risk of adverse clinical events following percutaneous coronary intervention: insights from the prospective, randomised TWENTE trial

Lam MK, Tandjung K, Sen H, Basalus MW, van Houwelingen KG, Stoel MG, Louwerenburg JW, Linssen GC, Said SA, Nienhuis MB, de Man FH, van der Palen J, von Birgelen C

Aims: To investigate the prognostic value of coronary dominance for various adverse clinical events following the implantation of drug-eluting stents.
Methods and results: We assessed two-year follow-up data of 1,387 patients from the randomised TWENTE trial. Based on the origin of the posterior descending coronary artery, coronary circulation was categorised into left and non-left dominance (i.e., right and balanced). Target vessel-related myocardial infarction (MI) was defined according to the updated Academic Research Consortium (ARC) definition (2x upper reference limit of creatine kinase [CK], confirmed by CK-MB elevation), and periprocedural MI (PMI) as MI </=48 hours following PCI. One hundred and thirty-six patients (9.8%) had left and 1,251 (90.2%) non-left dominance. Target lesions were more frequently located in dominant arteries (p<0.005). Left dominance was associated with more severe calcifications (p=0.006) and more bifurcation lesions (p=0.031). Non-left dominance tended to be less frequent in men (p=0.09). Left coronary dominance was associated with more target vessel-related MI (14 [10.3%] vs. 62 [5.0%], p=0.009). Left dominance independently predicted PMI (adjusted HR 2.19, 95% CI: 1.15-4.15, p=0.017), while no difference in other clinical endpoints was observed between dominance groups.
Conclusions: In the population of the TWENTE trial, we observed a higher incidence of periprocedural myocardial infarction in patients who had left coronary dominance.

Gepubliceerd: EuroIntervention 2015;11(2):180-7
Impact factor: 3.769

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13. Patient satisfaction and amenorrhea rate after endometrial ablation by ThermaChoice III or NovaSure: a retrospective cohort study

Muller I, van der Palen J, Massop-Helmink D, Vos-de Bruin R, Sikkema JM

Heavy menstrual bleeding poses an important health problem, which can be managed, besides other treatments, with endometrial ablation. Nowadays, the bipolar radio frequency device (NovaSure) is the most commonly used device for endometrial ablation, followed by the thermal balloon device (ThermaChoice III). Thus far, studies looking at treatment outcomes have mainly been done comparing NovaSure with the older ThermaChoice (I–II) devices. The aim of this study is to compare the effectiveness of the improved ThermaChoice III with NovaSure. Patients treated with ThermaChoice III at the Ziekenhuisgroep Twente hospital and NovaSure at the Medisch Spectrum Twente hospital were included in the study. The primary outcome measure was patient satisfaction after treatment, measured by the condition-specific menorrhagia multi-attribute scale (MMAS). The secondary

outcome measure was effectiveness of the treatment, measured by the amenorrhea rate and the hysterectomy rate. Five hundred fourteen patients were included in this study; of these, 216 patients were treated with ThermaChoice III and 289 patients with NovaSure. The score on the condition-specific MMAS was high for both groups, without a significant difference between the groups (88.8 vs 86.5, p?=?0.183). The amenorrhea rate was significantly higher in the NovaSure group (45 vs 27 %, p?=?0.001). The hysterectomy rate was slightly higher in the ThermaChoice III group, without a significant difference between the groups (19 compared to 13 %, p?=?0.066). Patient satisfaction is comparable in patients treated with ThermaChoice III or NovaSure. However, NovaSure endometrial ablation leads to a significantly higher amenorrhea rate.

Gepubliceerd: Gynecol Surg 2015;12(81):87
Impact factor: 0

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14. Safety and tolerability of nebulized amoxicillin + clavulanic acid in patients with stable COPD
Nijdam LC, Kuijvenhoven JC, van der Valk PD, Brusse-Keizer MG, van der palen J, Movig KL

Objective: To study the safety and tolerability of nebulized amoxicillin + clavulanic acid in patients with stable copd. Acute exacer- bations in copd are often treated with antibiotics. Previous studies showed ineffective amoxicillin concentrations in sputum in two thirds of the patients treated with systemic amoxicillin + clavulanic acid. Local administration, theo r- etically providing higher concentrations, has not been described before.
Design: Prospective observational intervention study.
Methods: Nine subjects received ascending doses amoxicillin + clavulanic acid, ranging from 50 + 10 mg up to 300 + 60 mg. Plasma and expectorated sputum samples were assayed for amoxicillin content. Safety was evaluated by spirometry before and after nebulization. Tolerability was evaluated by questionnaire.
Results: Spirometry showed no clinically relevant reduction in fev1 after nebulization with amoxicillin + clavulanic acid. In 34 nebulizations only 3 mild adverse events occurred. The sputum amoxicillin quantification showed levels well above mic90, while no effective levels were found in plasma.
Conclusion: Inhalation of nebulized amoxicillin + clavulanic acid is safe and well tolerated. Nebulized amoxicillin + clavulanic acid produces sputum concentrations well above mic with low systemic exposure.

Gepubliceerd: PW Wetenschappelijk Platform. 2015;9:a1510
Impact factor: 0

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15. Identifying key domains of health-related quality of life for patients with chronic obstructive pulmonary disease: interviews with healthcare professionals
Paap MC, Bode C, Lenferink LI, Terwee CB, van der Palen J

Purpose: The aim of this paper is to identify which domains of health-related quality of life (HRQoL) are most important for patients with chronic obstructive pulmonary disease (COPD), from the perspective of healthcare professionals (HCPs).
Methods: Thirteen Dutch HCPs [six pulmonologists, three pulmonology nurse practitioners, two physiotherapists and two general practitioners; 9 men; mean age 51.0 (SD = 10.6) years; mean years of experience 12.1 (SD = 7.2)] specialized in the field of COPD were recruited. The only inclusion criterion was that the HCP had to have extensive experience in treating COPD patients. The face-to-face interviews took 30-40 min.
Results: Physical health emerged as the most important theme from the spontaneous statements that HCPs made when asked about HRQoL in relation to COPD, closely followed by social health and coping with COPD-related complaints and restrictions. The most frequently selected PROMIS domains were fatigue, physical function, emotional support and depression. If the related domains satisfaction with participation in social roles and activities and ability to participate in social roles and activities were to be combined, it would come in second place after fatigue.
Conclusion: When comparing the domains chosen by HCPs to the ones chosen by patients in a recent study, there is a high degree of agreement, with the exception of depression. We argue that it is important to take into account both patient and HCP perspective when developing/selecting HRQoL instruments. Our results may be used to inform domain selection to measure HRQoL in patients with COPD, as well as instrument development.

Gepubliceerd: Qual Life Res 2015;24(6):1351-67
Impact factor: 2.486

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16. The St George's Respiratory Questionnaire revisited: a psychometric evaluation
Paap MC, Brouwer D, Glas CA, Monninkhof EM, Forstreuter B, Pieterse ME, van der Palen J

Purpose: The St George's Respiratory Questionnaire (SGRQ) has clearly acquired the status of legacy questionnaire for measuring health-related quality of life in patients with chronic obstructive pulmonary disease (COPD). The main aim of this study was to assess the underlying dimensionality of the SGRQ and to investigate the added value of the empirical weights used to calculate total scores.
Methods: The official Dutch translation of the SGRQ was completed by 444 COPD patients participating in two clinical studies. These data were used for secondary data analysis in this study. Three complementary statistical methods were used to assess dimensionality: Mokken scale analysis (MSA), parametric multidimensional item response theory (IRT) and bifactor analysis. Additionally, the original SGRQ weighting procedure was compared to IRT-based weighting.
Results: The results of the MSA and multidimensional item response theory (MIRT) pointed toward a unidimensional structure. The bifactor analyses indicated that there was a strong general factor, but the group factors did have additional value.

Nineteen items performed poorly in the MSA, MIRT analysis or both. Shortening the scale from 50 to 31 items did not negatively impact measurement precision. SGRQ total score and IRT-derived scores correlated strongly, 0.90 for the one-parameter model and 0.99 for the two-parameter model.
Conclusion: The SGRQ contains some multidimensionality, but an abbreviated version can be used as a unidimensional tool in patients with COPD. Subscale scores should be used with care. SGRQ total scores correlated highly with IRT-based scores, and thus, the weighting methods may be used interchangeably to calculate total scores.

Gepubliceerd: Qual Life Res 2015;244(1):67-79
Impact factor: 2.486

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17. Value of a multidisciplinary team for patients with a urological malignancy
Pelikaan L, Vriesema JL, Brusse-Keizer MG, Cornel EB

Objective: To evaluate degree of agreement between treatment proposals from urologist and a multidisciplinary team (MDT) for patients with an urological malignancy.
Design: Retrospective cohort study. METHOD: All letters from patients with an urological malignancy of prostate, bladder, kidney or testicle who were discussed at the MDT in Ziekenhuisgroep Twente from January 2011 until January 2013 were collected. This study studied the level and frequency of agreement between treatment proposals from urologist and MDT. Level of agreement was expressed by using Cohen's Kappa. Also treatments proposed by the MDT were compared to the final treatment choice of the patient.
Results: A total of 788 letters were analysed. For 9%, the MDT disagreed with the treatment recommended by the urologist. This disagreement was most often observed in patients with malignancy of kidney (kappa: 0.507; $p < 0.001$). Agreement for patients with malignancy of bladder, testicle and prostate were substantial (respectively kappa: 0.719; $p < 0.001$, kappa: 0.803; $p < 0.001$, kappa: 0.634; $p < 0.001$). Treatment proposals "brachytherapy" and "external radiotherapy" for prostate malignancy showed only moderate agreement (kappa: 0.564 and kappa: 0.568; $p < 0.001$ respectively). 93% of all patients elected to take (one of) the treatment proposals made by the MDT.
Conclusion: A multidisciplinary approach seems particularly useful for patients with malignancy of kidney. The additative value of MDT was less visible for patients with malignancy of prostate, which could be due to less consistent guidelines. Final treatment decision might be influenced by explanation and guidance of the treating urologist.

Gepubliceerd: Ned Tijdschr Geneeskd 2015;159:A8590
Impact factor: 0

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18. N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) Levels are Increased in Patients With Transient Ischemic Attack Accompanied by Nonfocal Symptoms
Plas GJ, Jurg SD, Brusse-Keizer M, Dippel DW, Koudstaal PJ, den Hertog HM

Background: Transient nonfocal neurological symptoms may serve as markers of cardiac dysfunction. We assessed whether serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, a biomarker of cardiac disease, are increased in patients with transient ischemic attack (TIA) accompanied by nonfocal symptoms and in patients with attacks of nonfocal symptoms (transient neurological attack [TNA]).
Methods and Results: We included 15 patients with TNA, 69 with TIA accompanied by nonfocal symptoms, 58 with large-vessel TIA, 32 with cardioembolic TIA, and 46 age- and sex-matched healthy control participants. Serum NT-proBNP levels were determined within 1 week after the attack. We compared log-transformed NT-proBNP levels of patients with cardioembolic TIAs and mixed or nonfocal TNAs, with those of patients with noncardioembolic TIAs as a reference group. Adjustments for age, sex, atrial fibrillation, and a history of nonischemic heart disease were made with a multiple linear regression model. Compared with large-vessel TIA (mean 14.2 pmol/L), mean NT-proBNP levels were significantly higher in patients with TIA accompanied by nonfocal symptoms (40.5 pmol/L, P=0.049) and with cardioembolic TIA (123.5 pmol/L; P=0.004) after adjustments for age, sex, atrial fibrillation, and a history of nonischemic heart disease. Patients with TNA also had higher mean NT-proBNP levels (20.8 pmol/L, P=0.38) than those with large-vessel TIA, but this difference was not statistically significant.
Conclusion: NT-proBNP levels are increased in patients with TIA accompanied by nonfocal symptoms.

Gepubliceerd: J Am Heart Assoc 2015;4(12)4.306
Impact factor: 4.306

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19. Comparison of 2 Dosages of Intraarticular Triamcinolone for the Treatment of Knee Arthritis: Results of a 12-week Randomized Controlled Clinical Trial
Popma JW, Snel FW, Haagsma CJ, Brummelhuis-Visser P, Oldenhof HG, van der Palen J, van de Laar MA

Objective: To determine whether a double dose of intraarticular triamcinolone acetonide is more effective for knee arthritis than a 40-mg dose.
Methods: In this 12-week randomized controlled clinical trial, 40 mg and 80 mg of intraarticular triamcinolone acetonide were compared in patients with knee arthritis. Evaluated variables included a Likert burden scale, visual analog scale pain scale, degree of arthritis activity, presence of swelling, and presence of functional limitation.
Results: Ninety-seven patients were randomized. No significant differences were observed between the groups regarding any outcomes.

Conclusion: An 80-mg dose of triamcinolone acetonide had no additional benefit compared with 40 mg as treatment for knee arthritis.
Trial registration: Nederlands Trial Register; trial registration number: NTR2298.

Gepubliceerd: J Rheumatol 2015 Aug 1;42(10):1865-8
Impact factor: 3.187

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20. A 9-month follow-up of a 3-month web-based alcohol treatment program using intensive asynchronous therapeutic support
Postel MG, Ter Huurne ED, de Haan HA, van der Palen J, De Jong CA

Background: Web-based alcohol interventions have demonstrated efficacy in randomized controlled trials. However, most studies have involved self-help interventions without therapeutic support.
Objectives: To examine the results of a 3-month web-based alcohol treatment program using intensive, asynchronous (non-simultaneous) therapeutic support (www.alcoholdebaas.nl) at 9-month follow-up assessment.
Methods: This study reports the follow-up results of 144 problem drinking participants who received a web-based alcohol treatment program. We investigated whether the intervention effects at treatment completion (3 months) continued to exist at 6 and 9 months of follow-up. The primary outcome measure was weekly alcohol consumption. Repeated measures analysis with a mixed model approach was used to address loss to follow-up.
Results: Weekly alcohol consumption significantly improved between baseline and 9 months ($F(1,74) = 85.6$, $p < 0.001$). Post-hoc tests revealed that the reduction occurred during the first 3 months (from 39.9-11.4 standard units a week). Although alcohol consumption had risen to 19.5 units per week at 9 months, it still decreased by more than 20 units compared to baseline drinking. Significant improvements with medium to large effect sizes were found on the secondary outcomes (depression, general health, and quality of life) at 9 months.
Conclusion: The web-based alcohol treatment with intensive asynchronous therapeutic support has been shown to be effective in reducing alcohol consumption and improving health status at post treatment assessments. The present study showed that most of these improvements were sustained after 9 months. Despite the lack of a control group and the high dropout rate, our findings suggest that web-based treatment can achieve relevant health gains in the long term.

Gepubliceerd: Am J Drug Alcohol Abuse 2015 Jun 18;1-8
Impact factor: 1.779

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21. Assessment of infection in chronic wounds based on the monitoring of elastase, lysozyme and myeloperoxidase activities
Schiffer D, Blokhuis-Arkes M, van der Palen J, Sigl E, Heinzle A, Guebitz GM

Infection in wounds affects about 2% of the population in developed countires at least once in their lifetime, and the lack of tools for its rapid diagnosis is still a

problem. Standard procedures of infection detection include the judgement of the classical clinical signs, the detection of signals specific to secondary wounds, or the quantification of the microbial load. The determination of the microbial load is a time-consuming standard procedure, although the presence of microbes per se is not indicative of infection.

Gepubliceerd: Br J Dermatol 2015 May 12;173(6):1529-31
Impact factor: 4.275

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22. The Preoperative CT-Scan Can Help to Predict Postoperative Complications after Pancreatoduodenectomy
Schroder FF, de Graaff F, Bouman DE, Brusse-Keizer M, Slump KH, Klaase JM

After pancreatoduodenectomy, complication rates are up to 40%. To predict the risk of developing postoperative pancreatic fistula or severe complications, various factors were evaluated. 110 consecutive patients undergoing pancreatoduodenectomy at our institute between January 2012 and September 2014 with complete CT scan were retrospectively identified. Pre-, per-, and postoperative patients and pathological information were gathered. The CT scans were analysed for the diameter of the pancreatic duct, attenuation of the pancreas, and the visceral fat area. All data was statistically analysed for predicting POPF and severe complications by univariate and multivariate logistic regression analyses. The POPF rate was 18%. The VFA measured at umbilicus (OR 1.01; 95% CI = 1.00-1.02; P = 0.011) was an independent predictor for POPF. The severe complications rate was 33%. Independent predictors were BMI (OR 1.24; 95% CI = 1.10-1.42; P = 0.001), ASA class III (OR 17.10; 95% CI = 1.60-182.88; P = 0.019), and mean HU (OR 0.98; 95% CI = 0.96-1.00; P = 0.024). In conclusion, VFA measured at the umbilicus seems to be the best predictor for POPF. BMI, ASA III, and the mean HU of the pancreatic body are independent predictors for severe complications following PD.

Gepubliceerd: Biomed Res Int 2015;2015:824525
Impact factor: 1.579

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23. Is the Eating Disorder Questionnaire-Online (EDQ-O) a valid diagnostic instrument for the DSM-IV-TR classification of eating disorders?
Ter Huurne ED, de Haan HA, Ten Napel-Schutz MC, Postel MG, Menting J, van der Palen J, Vroling MS, De Jong CA

Background: The Eating Disorder Questionnaire-Online (EDQ-O) is an online self-report questionnaire, which was developed specifically to provide a DSM-IV-TR classification of anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED), and eating disorder not otherwise specified (EDNOS), without using a face-to-face clinical interview.
Objective: The purpose of the present study was to examine the psychometric quality of the EDQ-O.

Methods: The validity of the EDQ-O was determined by examining the agreement with the diagnoses obtained from the Longitudinal, Expert, and All DATA (LEAD) standard. Participants included 134 new patients of a specialist center for eating disorders located in the Netherlands.
Results: Assessment of the validity of the EDQ-O yielded acceptable to good AUC (area under the receiver operating characteristic curve) values with a range from 0.72 to 0.83. Most other diagnostic efficiency statistics were also good except for a low sensitivity for AN (0.44), a low positive predictive value for BN (0.50), and a relatively low sensitivity for BED (0.66).
Conclusion: The results of the present study suggest that the EDQ-O performs acceptably as a diagnostic instrument for all DSM-IV-TR eating disorder classifications. However, suggestions are made to further improve the validity of the EDQ-O.

Gepubliceerd: Compr Psychiatry 2015;57:167-76
Impact factor: 2.252

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24. Web-Based Cognitive Behavioral Therapy for Female Patients With Eating Disorders: Randomized Controlled Trial
Ter Huurne ED, de Haan HA, Postel MG, van der Palen J, Van Der Nagel JE, De Jong CA

Background: Many patients with eating disorders do not receive help for their symptoms, even though these disorders have severe morbidity. The Internet may offer alternative low-threshold treatment interventions.
Objective: This study evaluated the effects of a Web-based cognitive behavioral therapy (CBT) intervention using intensive asynchronous therapeutic support to improve eating disorder psychopathology, and to reduce body dissatisfaction and related health problems among patients with eating disorders.
Methods: A two-arm open randomized controlled trial comparing a Web-based CBT intervention to a waiting list control condition (WL) was carried out among female patients with bulimia nervosa (BN), binge eating disorder (BED), and eating disorders not otherwise specified (EDNOS). The eating disorder diagnosis was in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, and was established based on participants' self-report. Participants were recruited from an open-access website, and the intervention consisted of a structured two-part program within a secure Web-based application. The aim of the first part was to analyze participant's eating attitudes and behaviors, while the second part focused on behavioral change. Participants had asynchronous contact with a personal therapist twice a week, solely via the Internet. Self-report measures of eating disorder psychopathology (primary outcome), body dissatisfaction, physical health, mental health, self-esteem, quality of life, and social functioning were completed at baseline and posttest.
Results: A total of 214 participants were randomized to either the Web-based CBT group (n=108) or to the WL group (n=106) stratified by type of eating disorder (BN: n=44; BED: n=85; EDNOS: n=85). Study attrition was low with 94% of the participants completing the posttest assignment. Overall, Web-based CBT showed a

significant improvement over time for eating disorder psychopathology (F97=63.07, P<.001, d=.82) and all secondary outcome measures (effect sizes between d=.34 to d=.49), except for Body Mass Index. WL participants also improved on most outcomes; however, effects were smaller in this group with significant between-group effects for eating disorder psychopathology (F201=9.42, P=.002, d=.44), body dissatisfaction (F201=13.16, P<.001, d=.42), physical health (F200=12.55, P<.001, d=.28), mental health (F203=4.88, P=.028, d=.24), self-esteem (F202=5.06, P=.026, d=.20), and social functioning (F205=7.93, P=.005, d=.29). Analyses for the individual subgroups BN, BED, and EDNOS showed that eating disorder psychopathology improved significantly over time among Web-based CBT participants in all three subgroups; however, the between-group effect was significant only for participants with BED (F78=4.25, P=.043, d=.61).
Conclusions: Web-based CBT proved to be effective in improving eating disorder psychopathology and related health among female patients with eating disorders.
Trial registration: Nederlands Trial Register (NTR): NTR2415; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2415 (Archived by WebCite at http://www.webcitation.org/6T2io3DnJ).

Gepubliceerd: J Med Internet Res 2015;17(6):e152
Impact factor: 3.428

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25. How does injury compensation affect health and disability in patients with complaints of whiplash? A qualitative study among rehabilitation experts-professionals
van der Meer S, Pieterse M, Reneman M, Verhoeven J, van der Palen J

Purpose: To explore rehabilitation professionals' opinions about the influence and the pathways of injury compensation (IC) on health and disability in patients with whiplash associated disorder (WAD).
Methods: Semi-structured interviews were performed among a purposeful selected sample of Dutch expert-professionals in the field of rehabilitation of patients with WAD. Inclusion continued until saturation was reached. Inductive and deductive thematic analyses were performed.
Results: Ten rehabilitation expert-professionals (five females), working as physician, psychologist or physiotherapist, were interviewed. All expert-professionals acknowledged that IC can influence rehabilitation, health and disability. The expert-professionals provided three causal pathways; a pathway through prolonged distress, a behavioral pathway, and patient characteristics that may either attenuate or worsen their response. They assess the influence of IC mainly with interview techniques. Most professionals discuss the potential influence of IC with their patients, because they want to give clear information to the patient. Some emphasize that their role is neutral in relation with the IC. Others mention that financial consequences can accompany functional improvement.
Conclusions: Rehabilitation expert-professionals believe that IC may affect rehabilitation, health and disability in patients with WAD. Three pathways are mentioned by the experts-professionals. Implications for Rehabilitation According to rehabilitation expert-professionals, an injury compensation (IC) can lead to distress,

by creating a (conscious or unconscious) conflict of interests within a patient between striving for compensation on one hand, and recovery on the other hand. Patient characteristics can either attenuate or worsen IC-related distress. Reliable and valid tools need to be developed to assess the influence of IC on health, disability and rehabilitation, and to limit the negative effects. Rehabilitation professionals can discuss the possible unintended effects of IC with their patients to clarify their current situation.

Gepubliceerd: Disabil Rehabil 2015 Apr 14;1-7
Impact factor: 1.985

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26. Effect of weight loss, with or without exercise, on body composition and sex hormones in postmenopausal women: the SHAPE-2 trial

van Gemert WA, Schuit AJ, van der Palen J, May AM, Iestra JA, Wittink H, Peeters PH, Monninkhof EM

I**ntroduction:** Physical inactivity and overweight are risk factors for postmenopausal breast cancer. The effect of physical activity may be partially mediated by concordant weight loss. We studied the effect on serum sex hormones, which are known to be associated with postmenopausal breast cancer risk, that is attributable to exercise by comparing randomly obtained equivalent weight loss by following a hypocaloric diet only or mainly by exercise.
Methods: Overweight, insufficiently active women were randomised to a diet (N = 97), mainly exercise (N = 98) or control group (N = 48). The goal of both interventions was to achieve 5-6 kg of weight loss by following a calorie-restricted diet or an intensive exercise programme combined with only a small caloric restriction. Primary outcomes after 16 weeks were serum sex hormones and sex hormone-binding globulin (SHBG). Body fat and lean mass were measured by dual-energy X-ray absorptiometry.
Results: Both the diet (-4.9 kg) and mainly exercise (-5.5 kg) groups achieved the target weight loss. Loss of body fat was significantly greater with exercise versus diet (difference -1.4 kg, P < 0.001). In the mainly exercise arm, the reduction in free testosterone was statistically significantly greater than that of the diet arm (treatment effect ratio [TER] 0.92, P = 0.043), and the results were suggestive of a difference for androstenedione (TER 0.90, P = 0.064) and SHBG (TER 1.05, P = 0.070). Compared with the control arm, beneficial effects were seen with both interventions, diet and mainly exercise, respectively, on oestradiol (TER 0.86, P = 0.025; TER 0.83, P = 0.007), free oestradiol (TER 0.80, P = 0.002; TER 0.77, P < 0.001), SHBG (TER 1.14; TER 1.21, both P < 0.001) and free testosterone (TER 0.91, P = 0.069; TER = 0.84, P = 0.001). After adjustment for changes in body fat, intervention effects attenuated or disappeared.
Conclusions: Weight loss with both interventions resulted in favourable effects on serum sex hormones, which have been shown to be associated with a decrease in postmenopausal breast cancer risk. Weight loss induced mainly by exercise additionally resulted in maintenance of lean mass, greater fitness, greater fat loss and a larger effect on (some) sex hormones. The greater fat loss likely explains the observed larger effects on sex hormones.

Trial registration: ClinicalTrials.gov identifier: NCT01511276. Registered on 12 January 2012.

Gepubliceerd: Breast Cancer Res 2015;17(1):120
Impact factor: 5.490

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27. Quality of Life after Diet or Exercise-Induced Weight Loss in Overweight to Obese Postmenopausal Women: The SHAPE-2 Randomised Controlled Trial
van Gemert WA, van der Palen J, Monninkhof EM, Rozeboom A, Peters R, Wittink H, Schuit AJ, Peeters PH

Introduction: This study investigates the effect of a modest weight loss either by a calorie restricted diet or mainly by increased physical exercise on health related quality of life (HRQoL) in overweight-to-obese and inactive postmenopausal women. We hypothesize that HRQoL improves with weight loss, and that exercise-induced weight loss is more effective for this than diet-induced weight loss.
Methods: The SHAPE-2 trial was primarily designed to evaluate any additional effect of weight loss by exercise compared with a comparable amount of weight loss by diet on biomarkers relevant for breast cancer risk. In the present analysis we focus on HRQoL. We randomly assigned 243 eligible women to a diet (n = 97), exercise (n = 98), or control group (n = 48). Both interventions aimed for 5-6 kg weight loss. HRQoL was measured at baseline and after 16 weeks by the SF-36 questionnaire.
Results: Data of 214 women were available for analysis. Weight loss was 4.9 kg (6.1%) and 5.5 kg (6.9%) with diet and exercise, respectively. Scores of the SF-36 domain 'health change' increased significantly by 8.8 points (95% CI 1.6;16.1) with diet, and by 20.5 points (95% CI 13.2;27.7) with exercise when compared with control. Direct comparison of diet and exercise showed a statistically significantly stronger improvement with exercise. Both intervention groups showed a tendency towards improvements in most other domains, which were more pronounced in the exercise group, but not statistically different from control or each other.
Conclusion: In a randomized trial in overweight-to-obese and inactive postmenopausal women a comparable 6%-7% weight loss was achieved by diet-only or mainly by exercise and showed improvements in physical and mental HRQoL domains, but results were not statistically significant in either the diet or exercise group. However, a modest weight loss does lead to a positive change in self-perceived health status. This effect was significantly larger with exercise-induced weight loss than with comparable diet-induced weight loss.
Trial registration: ClinicalTrials.gov NCT01511276.

Gepubliceerd: PLoS One 2015;10(6):e0127520
Impact factor: 3.234

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28. Protective effect of a low single dose inhaled steroid against exercise induced bronchoconstriction
Visser R, Wind M, de Graaf B, de Jongh FH, van der Palen J, Thio BJ

Objective: Daily use of inhaled corticosteroids (ICS) reduces exercise induced bronchoconstriction (EIB) in asthmatic children. A high single dose of ICS also provided acute protection against EIB. Objective of this study is to investigate whether a low single dose of ICS offers protection against EIB in asthmatic children.
Methods: 31 Mild asthmatic children not currently treated with inhaled corticosteroids, 5-16 years, with EIB (fall in FEV0.5/1 >/= 13%) were included in a prospective intervention study. They performed two ECT's within 2 weeks. Four hours before the second test children inhaled 200 mug beclomethasone-dipropionate (BDP) with a breath-actuated inhaler (BAI).
Results: The median fall in FEV0.5/1 after 200 mug BDP was significantly reduced from 30.9% at baseline to 16.0% (P < 0.001). Twenty children (64.5%) showed a good response to 200 mug BDP (>/=50% decrease in fall of FEV0.5/1), while 8 children showed a moderate response (25-50%), and three children showed no response at all (< 25%).
Conclusion: A low single dose ICS offers acute protection against EIB in the majority of asthmatic children not currently treated with inhaled corticosteroids.

Gepubliceerd: Pediatr Pulmonol 2015;50(12):1178-83
Impact factor: 2.704

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29. Reversibility after inhaling salbutamol in different body postures in asthmatic children: A pilot study
Visser R, van der Palen J, de Jongh FH, Thio BJ

Rationale: Pulmonary medication is mostly delivered in the form of medical aerosols to minimize systemic side effects. A major drawback of inhaled medication is that the majority of inhaled particles impacts in the oropharynx at the sharp bend of the airway. Stretching the airway by a forward leaning body posture with the neck extended ("sniffing position") may improve pulmonary deposition and clinical effects.
Methods: 41 asthmatic children who were planned for standard reversibility testing at the pulmonary function lab, alternately inhaled 200 mugr salbutamol with an Autohaler((R)) in the standard or in the forward leaning body posture. Forced Expiratory Volume in 1 s (FEV1), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF), Mean Expiratory Flow at 25% of vital capacity (MEF25) and Mean Expiratory Flow at 75% of vital capacity (MEF75) were analysed.
Results: The children in the forward leaning body posture group showed a significantly higher mean FEV1 reversibility than the control group after inhalation of 200 mugr salbutamol (10.2% versus 4.1%, p = 0.019). Additionally, mean MEF75 was significantly more reversible in the forward leaning body posture group versus the standard body posture group (32.2% resp. 8.9%, p = 0.013).
Conclusion: This pilot study showed a higher reversibility of FEV1 and MEF75 after inhaling salbutamol in a forward leaning body posture compared to the standard body posture in asthmatic children. This suggests that pulmonary effects of salbutamol can be improved by inhaling in a forward leaning body posture with the neck extended. This effect is possibly due to a higher pulmonary deposition of salbutamol and should be confirmed in a randomized controlled trial.

Gepubliceerd: Respir Med 2015 Apr;109(4):459-62
Impact factor: 3.086

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30. Reversibility of pulmonary function after inhaling salbutamol in different doses and body postures in asthmatic children
Visser R, Kelderman S, de Jongh FH, van der Palen J, Thio BJ

Rationale: Pulmonary medication is often delivered in the form of medical aerosols designed for inhalation. Recently, breath actuated inhalers (BAI's) gained popularity as they can be used without spacers. A major drawback of BAI's is the impaction in the upper airway. Stretching the upper airway by a forward leaning body posture with the neck extended ("sniffing position") during inhalation may reduce upper airway impaction and improve pulmonary deposition. Aim of this study was to investigate the reversibility of lung function with different doses salbutamol inhaled with a BAI in the forward leaning posture compared to the standard posture in asthmatic children.
Methods: 22 clinically stable asthmatic children, 5-14 years old, performed four reversibility measurements. Children inhaled 200 mug or 400 mug salbutamol with a BAI in the standard or in the forward leaning posture with the neck extended in a randomized single-blinded cross-over design.
Results: Reversibility of lung function after inhaling salbutamol in the forward leaning posture was not significantly different compared to inhalation in the standard posture. Mean FEV1 reversibility was significantly greater after inhaling 400 mug salbutamol compared to 200 mug salbutamol in the standard posture (9.4% +/- 9.5% versus 4.5% +/- 7.5%, difference 4.9% (95CI 0.9; 9.0%); p = 0.021).
Conclusion: In clinically stable asthmatic children, inhalation of salbutamol with a BAI in a forward leaning posture does not increase reversibility of lung function. Inhalation of 400 mug compared to 200 mug salbutamol with a BAI does improve reversibility.

Gepubliceerd: Respir Med 2015 Jul 23;109(10):1274-9
Impact factor: 3.086

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31. The effect of body posture during medication inhalation on exercise induced bronchoconstriction in asthmatic children
Visser R, Wind M, de Graaf BJ, de Jongh FH, van der Palen J, Thio BJ

Rationale: Inhaling medication in a standard body posture leads to impaction of particles in the sharp angle of the upper airway. Stretching the upper airway by extending the neck in a forward leaning body posture may improve pulmonary deposition. A single dose of inhaled corticosteroids (ICS) offers acute, but moderate protection against exercise induced bronchoconstriction (EIB). This study investigated whether inhaling a single dose of ICS in a forward leaning posture improves this protection against EIB.

Methods: 32 Asthmatic children, 5-16 years, with EIB (Median fall in FEV1 or FEV0.5 30.9%) performed two exercise challenge tests (ECT's) with spirometry in a single blinded cross-over trial design. Children inhaled a single dose of 200 mug beclomethasone dipropionate (BDP) 4 h before the ECT, once in the standard posture and once with the neck extended in a forward leaning posture. Spirometry was also performed before the inhalation of the single dose of BDP.
Results: Inhalation of BDP in both body postures provided similar protection against EIB (fall in FEV1 or FEV0.1 in standard posture 16.7%; in forward leaning posture 15.1%, p = 0.83). Inhaling ICS in a forward leaning posture significantly delayed EIB compared to inhaling in the standard posture (respectively 2.5 min +/- 1.0 min vs. 1.6 min +/- 0.8 min; difference 0.9 min (95CI 0.25; 1.44 min); p = 0.01).
Conclusion: Inhalation of a single dose BDP in both the forward leaning posture and the standard posture provided effective and similar protection against EIB in asthmatic children, but the forward leaning posture resulted in a delay of EIB.
Register: NTR3432 (www.trialregister.nl).

Gepubliceerd: Respir Med 2015 Oct;109(10):1257-61
Impact factor: 3.086

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32. The impact of discussing exercise test results of young asthmatic children on adherence to maintenance medication
Visser R, Brusse-Keizer M, van der Palen J, Klok T, Thio BJ

Objective: Parents' awareness of their child's asthma may improve by discussing an exercise challenge test (ECT) result with them. We investigated the influence of discussing an ECT result with parents on adherence to inhaled maintenance medication, parental illness perceptions and medication beliefs in young asthmatic children.
Methods: A total of 79 children, 4-7 years old and enrolled in our standard comprehensive asthma care program, performed an ECT to assess exercise induced bronchoconstriction (EIB). The result of the ECT was immediately discussed with the parents. Median medication adherence level was measured with electronic medication loggers from six weeks before the ECT till six weeks afterwards. Parental beliefs about medicines and illness perceptions were measured with the Beliefs about Medicines Questionnaire (BMQ) and the Brief Illness Perceptions Questionnaire (B-IPQ).
Results: The median baseline adherence level was high (83%) and showed a small significant decline after the ECT. There was no significant difference in the decrease in median adherence level between the children with or without EIB. Most parents (82.1%) showed a positive necessity-concern ratio at baseline, as measured with the BMQ. There was no clinical relevant change in medication concerns and necessity scores or in illness perceptions.
Conclusion: Discussing ECT results with parents does not modify median adherence levels to inhaled maintenance medication nor medication beliefs of highly adherent young asthmatic children who are already enrolled in a comprehensive asthma care program.

Gepubliceerd: J Asthma 2015 May 18;52(7):743-8
Impact factor: 1.802

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33. Emphasizing of shaking the inhaler as part of inhalation instruction is important in young asthmatic children
Visser R, Brusse-Keizer MG, van der Palen J, Thio BJ

Background: Current guidelines recommend to monitor inhalation technique in asthmatic children every 3-6 months. The aim of this study was to investigate inhalation technique 6 weeks after instruction in young asthmatic children, using a pressurized metered dose inhaler with spacer.
Methods: 91 asthmatic children, 4-8 years, from our outpatient clinic, demonstrated their inhalation technique with a pressurized metered dose inhaler with spacer. Errors in inhalation technique were scored on an inhaler specific standardized checklist designed by the Dutch Lung Foundation. Afterwards, feedback on inhalation technique was provided to the child and his/her parent(s). Six weeks later their inhalation technique was reevaluated.
Results: Significantly more children carried out a perfect inhalation technique (67.0% vs. 36.3%, p=<0.001) and significantly less children showed one, two or three errors (31.5% vs. 63.7% p=<0.001) 6 weeks after instruction. Significantly more children failed to shake their inhaler 6 weeks after instruction (16.9% vs. 6.6%, p=0.035).
Conclusion: Although we observed a significant improvement in inhalation technique six weeks after instruction with tailored feedback, more young asthmatic children failed to shake their inhaler. We recommend that reinforcement on essential steps that are performed correctly should be highly emphasized.

Pediat Therapeut 2015;5(2):244
Impact factor: 0.314

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34. Arterial clamping leads to stenosis at clamp sites after femoropopliteal bypass surgery
Vriens BH, Pol RA, Hulsebos RG, van Det RJ, van der Palen J, Zeebregts CJ, Geelkerken RH

Background: To date, the incidence and clinical relevance of arterial stenosis at clamp sites after femoropopliteal bypass surgery is unknown.
Methods: Ninety-four patients underwent a femoropopliteal bypass in which the arterial inflow and outflow clamp sites were controlled by the Fogarty-Soft-Inlay clamp and marked with an hemoclip. The number of pre-existing atherosclerotic segments, clamp force, and clamp time were recorded and the occurrence of a stenosis at the clamp site was determined.
Results: After a mean follow-up of 83 months, a significant stenosis was confirmed at 23 of the 178 clamp sites (12.9%; 95% confidence interval 8.4 to 18.8). The mean number of pre-existing atherosclerotic segments (P = .28) and the mean clamp force (P = .55) was similar between the groups with and without a stenosis. There was a

significant difference regarding clamp time between the group with and without a stenosis (38 minutes and 26 minutes, P = .001).
Conclusion: Arterial clamping, even with the Fogarty-Soft-Inlay clamp, can lead to clamp stenosis and seems to be related to the duration of clamping, but not to pre-existent atherosclerotic burden.

Gepubliceerd: Am J Surg 2015 May 7;210(3):536-44
Impact factor: 2.291

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35. Cost-Effectiveness of a Community-Based Exercise Programme in COPD Self-Management
Zwerink M, Effing T, Kerstjens HA, van der Valk PD, Brusse-Keizer M, Zielhuis G, van der Palen J

I**ntroduction:** Information regarding cost-effectiveness of community-based exercise programmes in COPD is scarce. Therefore, we have investigated whether a community-based exercise programme is a cost-effective component of self-management for patients with COPD after 2 years of follow-up.
Methods: All included COPD patients participated in four self-management sessions. Additionally, patients in the COPE-active group participated in an 11-month community-based exercise programme led by physiotherapists. Patients trained 3 times/week for 6 months and two times/week during the subsequent 5 months. In both periods, one of these weekly training sessions was home-based (unsupervised). No formal physiotherapy sessions were offered to COPE-active patients in the second year. A decision analytical model with a 24-month perspective was used to evaluate cost-effectiveness. Incremental cost-effectiveness ratios (ICER) were calculated and cost-effectiveness planes were created.
Results: Data of 77 patients participating in the exercise programme and 76 patients in the control group were analysed. The ICER for an additional patient prevented from deteriorating at least 47.5 meters on the ISWT was euro6257. The ICER for an additional patient with a clinically relevant improvement (>/= 500 steps/day) in physical activity was euro1564, and the ICER for an additional quality-adjusted life year (QALY) was euro10 950.
Conclusion: Due to a lack of maintenance of beneficial effects on our primary outcome exercise capacity after 2 years of follow-up and higher costs of the programme, the community-based exercise programme cannot be considered cost-effective compared to self-management programmes only. Nevertheless, the ICERs for the secondary outcomes physical activity and QALY are generally considered acceptable.

Gepubliceerd: COPD 2015 Dec 1;1-10
Impact factor: 2.673

Totale impact factor: 88.549
Gemiddelde impact factor: 2.530

Aantal artikelen 1e, 2e of laatste auteur: 16
Totale impact factor: 40.896
Gemiddelde impact factor: 2.556

Neurochirurgie

1. A Two Center Comparative Study on Tonic Versus Burst Spinal Cord Stimulation: Amount of Responders and Amount of Pain Suppression
de Ridder D, Lenders MW, de Vos CC, Dijkstra-Scholten C, Wolters R, Vancamp T, Van Looy P, Van Havenbergh T, Vanneste S

I**ntroduction:** Spinal cord stimulation is a safe and effective procedure applied for medically intractable neuropathic pain and failed back surgery syndrome. Recently a novel stimulation paradigm was developed, called burst stimulation consisting of intermittent packets of closely spaced high frequency stimuli. The design consists of 40 Hz burst mode with 5 spikes at 500 Hz per burst, with a pulse width of 1 ms and 1 ms interspike interval delivered in constant current mode.
Methods and Materials: A retrospective analysis is performed looking at 102 patients from 2 neuromodulation centers, 1 in Belgium, 1 in The Netherlands. This consisted of 2 groups, 1 group who had become failures to tonic (conventional) stimulation, and 1 group who still responded to tonic stimulation. All patients were switched from tonic to burst stimulation and the amount of responders as well as the amount of pain suppression was assessed.
Results: Overall burst stimulation was significantly better than tonic stimulation and baseline. On average the pain on numeric rating scale (NRS) improved from 7.8 at baseline to 4.9 with tonic to 3.2 with burst stimulation. For the Belgian and Dutch centers combined 62.5% of non-responders to tonic stimulation did respond to burst stimulation, on average with 43% pain suppression. Most responders to tonic further improved with burst stimulation, on average pain suppression improved from 50.6% to 73.6.3%. The results (from both centers) did not differ for the amount of obtained pain suppression, only for the amount of responders, which could be related to the different profile of the 2 participating centers.
Conclusion: Burst seems to be significantly better than tonic stimulation. It can rescue an important amount of non-responders to tonic stimulation and can further improve pain suppression in responders to tonic stimulation.

Gepubliceerd: Clin J Pain 2015;31(5):433-7
Impact factor: 2.527

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2. Is Preoperative Pain Duration Important in Spinal Cord Stimulation? A Comparison Between Tonic and Burst Stimulation
de Ridder D, Vancamp T, Lenders MW, de Vos CC, Vanneste S

Objective: Conflicting data have been published as to whether the success rate of spinal cord stimulation (SCS) is inversely proportional to the time interval from the initial onset of symptoms to implantation. Recently, a new stimulation design called burst stimulation has been developed that seems to exert its effect by modulating both the medial and lateral pain pathways and has a better effect than tonic stimulation on global pain, back pain, and limb pain.

Materials and Methods: We analyzed the effect of preoperative pain duration on the degree of pain suppression by both tonic and burst stimulation in a group of patients (n = 49) who underwent both tonic and burst SCS.
Results: Using Pearson correlation analysis and controlling for age and duration of SCS, no correlation could be found between the preoperative pain duration and the success of SCS, either for tonic or for burst SCS, as defined by a numeric rating scale for pain. Using a different analysis method, dividing patients into groups according to preoperative pain duration, the same absence of influence was found. Pain was better suppressed by burst stimulation than tonic stimulation, irrespective of the preoperative pain duration.
Conclusions: These results suggest that the duration of pain is not an exclusion criterion for SCS and that similar success rates can be obtained for longstanding pain and pain of more recent onset.

Gepubliceerd: Neuromodulation 2015;18(1):13-7
Impact factor: 2.701

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3. Intermanual transfer in an artist with Parkinson's disease
Kho KH, Janssen N

A professional right-handed painter with Parkinson's disease (PD) broke his right arm and continued to paint with his left hand, showing an intact intermanual transfer of skills. This neurocognitive process is related to the supplementary motor area, a brain region that has also been shown to be involved in PD. This observation raises questions about the exact neural underpinnings of intermanual transfer and the possible impact of neurodegenerative disease and medication.

Gepubliceerd: Neurocase 2015 Jun 8;1-3
Impact factor: 1.124

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4. The effect of vagus nerve stimulation on cardiorespiratory parameters during rest and exercise
Mulders DM, de Vos CC, Vosman I, van Putten MJ

Purpose: Vagus nerve stimulation (VNS) has been successfully applied to reduce seizure frequency in numerous patients with epilepsy. However, various side effects, including dyspnea and bradycardia have been reported, that appear exercise related in some patients. This pilot study aims to obtain insight in the cardiorespiratory effects of VNS during both rest and exercise.
Methods: Patients with a VNS device who experience side effects during exercise are compared with patients without side effects. Respiratory and cardiac parameters measured during rest and exercise include heart rate, breathing frequency and tidal volume.
Results: Sixty-two episodes of VNS in five patients with and five patients without side effects were recorded. In addition, five control subjects have been measured. During rest, all subjects showed stable values for the cardiorespiratory parameters.

During the first minutes of exercise, heart rate, breathing frequency and tidal volume increased. Thereafter, a steady state was reached again for all subjects. During VNS episodes, eight out of 10 patients showed a small but consistent decrease in heart rate, along with an increase in breathing frequency in eight out of nine patients. Tidal volumes decreased during VNS episodes. These effects, induced by VNS, occurred during both rest and exercise. Magnitude of these effects varied between patients, but was not necessarily related to the intensity of the experienced side effects.
Conclusion: This pilot study shows that VNS causes an increase in breathing frequency and a decrease in tidal volume and heart rate in the majority of patients, during both rest and exercise.

Gepubliceerd: Seizure 2015 Oct 23;33:24-8
Impact factor: 1.822

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5. Authors' reply
Spaans HP, Sienaert P, Bouckaert F, van den Berg JF, Verwijk E, Kho KH, Stek ML, Kok RM

Gepubliceerd: Br J Psychiatry 2015 Feb;206(2):167-8
Impact factor: 7.991

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6. Speed of remission in elderly patients with depression: electroconvulsive therapy v. medication
Spaans HP, Sienaert P, Bouckaert F, van den Berg JF, Verwijk E, Kho KH, Stek ML, Kok RM

Background: Severe depression can be a life-threatening disorder, especially in elderly patients. A fast-acting treatment is crucial for this group. Electroconvulsive therapy (ECT) may work faster than medication.
Aims: To compare the speed of remission using ECT v. medication in elderly in-patients.
Method: The speed of remission in in-patients with a DSM-IV diagnosis of major depression (baseline MADRS score 20) was compared between 47 participants (mean age 74.0 years, s.d. = 7.4) from an ECT randomised controlled trial (RCT) and 81 participants (mean age 72.2 years, s.d. = 7.6) from a medication RCT (nortriptyline v. venlafaxine).
Results: Mean time to remission was 3.1 weeks (s.d. = 1.1) for the ECT group and 4.0 weeks (s.d. = 1.0) for the medication group; the adjusted hazard ratio for remission within 5 weeks (ECT v. medication) was 3.4 (95% CI 1.9-6.2).
Conclusions: Considering the substantially higher speed of remission, ECT deserves a more prominent position in the treatment of elderly patients with severe depression.

Gepubliceerd: Br J Psychiatry 2015;206(1):67-71
Impact factor: 7.991

7. Masking the Auditory Evoked Potential in TMS-EEG: A Comparison of Various Methods
ter Braack EM, de Vos CC, van Putten MJ

There is growing interest in combining transcranial magnetic stimulation (TMS) with electroencephalography (EEG). Because TMS pulses are accompanied by a clicking sound, it is very likely that part of the response in the EEG consists of an auditory evoked potential (AEP). Different methods have been applied to mask the sound of TMS. However, it is unclear which masking method is most effective in reducing the AEP. In this study we explore the presumed contribution of the AEP to the response and evaluate different ways to mask the TMS clicking sound. Twelve healthy subjects and one completely deaf subject participated in this study. Eight different masking conditions were evaluated in nine hearing subjects. The amplitude of the N100-P180 complex was compared between the different masking conditions. We were not able to completely suppress the N100-P180 when the coil was placed on top of the head. Using an earmuff or exposing the subjects to white or adapted noise caused a small but significant reduction in N100-P180 amplitude, but the largest reduction was achieved when combining a layer of foam, placed between coil and head, with white or adapted noise. The deaf subject also showed a N100-P180 complex. We conclude that both the TMS clicking sound and cortical activation by the magnetic pulse contribute to the N100-P180 amplitude.

Gepubliceerd: Brain Topogr 2015;28(3):520-8
Impact factor: 3.468

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8. Clinical Pedicle Screw Accuracy and Deviation From Planning in Robot-Guided Spine Surgery: Robot-Guided Pedicle Screw Accuracy
van Dijk JD, van den Ende RP, Stramigioli S, Kochling M, Höss N

Study Design: A retrospective chart review was performed for 112 consecutive minimally invasive spinal surgery patients who underwent pedicular screw fixation in a community hospital setting.
Objective: To assess the clinical accuracy and deviation in screw positions in robot-assisted pedicle screw placement.
Summary of background data: Accuracy of pedicle screw placement in in vivo studies varies widely, especially when minimally invasive techniques are used. Robotic guidance was recently introduced to increase screw placement accuracy but still reported accuracies vary.
Methods: Reproducibility of the surgeon's plan using robotic guidance was assessed by fusing individual vertebras from the preoperative computed tomography (CT) containing the planning with a postoperative CT. Deviation in entry point and difference in angle of insertion was measured on axial and sagittal planes. Grading of pedicle screw placement was performed on postoperative CTs using the Gertzbein-Robbins classification.

Results: CT-to-CT fusion succeeded for 178 screws, but these appeared to be random, with no apparent selection bias. Mean deviation in entry point was 2.0 +/- 1.2 mm. Mean difference in angle of insertion was 2.2 degrees +/- 1.7 degrees on the axial plane and 2.9 degrees +/- 2.4 degrees on the sagittal plane. Assessment of pedicle screw accuracy showed that 477 of 487 screws (97.9%) were safely placed (<2 mm, category A+B), 8 screws in category C and 1 in category D. None of the screws necessitated resurgery for revised placement.
Conclusion: Preoperative planning of robotic guidance is reproduced intraoperatively within acceptable deviations. We conclude that robotic guidance allows for highly accurate execution of the preoperative plan, leading to accurate screw placement.

Gepubliceerd: Spine (Phila Pa 1976) 2015 Sep 1;40(17):E986-E991
Impact factor: 2.297

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9. Relapse and long-term cognitive performance after brief pulse or ultrabrief pulse right unilateral electroconvulsive therapy: A multicenter naturalistic follow up
Verwijk E, Spaans HP, Comijs HC, Kho KH, Sienaert P, Bouckaert F, Obbels J, Scherder EJ, Stek ML, Kok RM

Background: Superior cognitive functioning for electroconvulsive therapy (ECT) with right unilateral (RUL) ultrabrief pulse (UBP) stimulation compared to RUL brief pulse (BP) stimulation is not clearly established and long-term data is needed.
Methods: We conducted a prospective naturalistic follow-up of 87 inpatients from three tertiary psychiatric hospitals. Before these patients entered the follow up phase, they had participated in a RCT comparing twice weekly RUL BP (1.0ms) with RUL UBP (0.3-0.4ms) ECT eight times seizure threshold until remission (MADRS<10), for a maximum of six weeks. Three and six months after the index ECT patients were monitored for relapse and cognitive performance (retrograde amnesia, semantic memory and lexical memory). We compared relapse rate and cognitive performance between RUL BP and RUL UBP stimulation.
Results: Of the 50 patients who remitted after index ECT 44 (24 BP; 20 UBP) were monitored for follow up. Relapse occurred in 25% of the BP group and in 25% of the UBP group (chi(2)=0.00, p=1.0) at three-month follow-up; whereas 43.5% of the BP group and 35% of the UBP group relapsed (chi(2)=0.322, p=0.57) at six months follow-up. Cognitive assessments (17 BP; 16 UBP) showed no significant differences between BP and UBP groups, except for an advantage for the BP group in the autobiographical incident questions at three months follow-up only (p=0.04; d=0.77).
Limitations: This study may be limited since relapse in a naturalistic follow-up can be influenced by medication and other unknown factors, like social support, medical comorbidity, and psychotherapy. The small numbers of our subgroups hamper statistical significance.
Conclusions: Patients that achieved remission after RUL BP or RUL UBP ECT showed similar relapse rates after three and six months. There was no cognitive advantage of UBP over BP ECT in follow up.

Clinical trials registration: Netherlands trial register www.trialregister.nl registration number NTR1304.

Gepubliceerd: J Affect Disord 2015 Sep 15;184:137-44
Impact factor: 3.383

Totale impact factor: 33.304
Gemiddelde impact factor: 3.700

Aantal artikelen 1e, 2e of laatste auteur: 5
Totale impact factor: 11.238
Gemiddelde impact factor: 2.238

Neurologie

1. Poststroke Epilepsy Is Associated With a High Mortality After a Stroke at Young Age: Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation Study
Arntz RM, Rutten-Jacobs LC, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, de Leeuw FE

Background and purpose: Poststroke epilepsy is a common complication after a young stroke. We investigated the association between poststroke epilepsy and mortality.
Methods: We performed a prospective cohort study among 631 patients with a first-ever transient ischemic attack or ischemic stroke, aged 18 to 50 years. Survival analysis and Cox proportional hazard analysis were used to estimate cumulative mortality and hazard ratios for patients with and without epilepsy.
Results: After mean follow-up of 12.5 years (SD 8.6), 76 (12.0%) developed poststroke epilepsy. Case fatality was 27.4% for patients with poststroke epilepsy and 2.1% for those without. Poststroke epilepsy was associated with 30-day mortality (hazard ratio, 4.8; 95% confidence interval, 1.7-14.0) and long-term mortality (hazard ratio, 1.8; 95% confidence interval, 1.2-2.9).
Conclusions: Epilepsy is a common problem after a young stroke and is associated with an increased short-term and long-term mortality.

Gepubliceerd: Stroke 2015 Aug;46(8):2309-11
Impact factor: 5.761

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2. Pneumoperitoneum after a bilateral pneumothorax
Beernink TM, van Vliet J

A 52-year-old male presented with a chief complaint of shortness of breath after lifting two heavy bags. After the increase in thoracic pressure by lifting the bags, air was released from the lungs by a spontaneous rupture of a bullae causing a bilateral pneumothorax. The increased intra-thoracic pressure caused air to pass through the oesophageal hiatus created by an oesophagectomy several years ago . By following the path of least resistance the air accumulated through the hiatus in the abdominal cavity causing a pneumoperitoneum. Our case history shows that understanding anatomical changes after surgery can give a clue to the diagnosis and in this case justify conservative management of a pneumoperitoneum.

Gepubliceerd: Neth J Crit Care 2015;23(5): 21
Impact factor: 0

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3. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke
Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals

J, Hofmeijer J, van Oostayen JA, Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW

Background: In patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion, intraarterial treatment is highly effective for emergency revascularization. However, proof of a beneficial effect on functional outcome is lacking.
Methods: We randomly assigned eligible patients to either intraarterial treatment plus usual care or usual care alone. Eligible patients had a proximal arterial occlusion in the anterior cerebral circulation that was confirmed on vessel imaging and that could be treated intraarterially within 6 hours after symptom onset. The primary outcome was the modified Rankin scale score at 90 days; this categorical scale measures functional outcome, with scores ranging from 0 (no symptoms) to 6 (death). The treatment effect was estimated with ordinal logistic regression as a common odds ratio, adjusted for prespecified prognostic factors. The adjusted common odds ratio measured the likelihood that intraarterial treatment would lead to lower modified Rankin scores, as compared with usual care alone (shift analysis).
Results: We enrolled 500 patients at 16 medical centers in the Netherlands (233 assigned to intraarterial treatment and 267 to usual care alone). The mean age was 65 years (range, 23 to 96), and 445 patients (89.0%) were treated with intravenous alteplase before randomization. Retrievable stents were used in 190 of the 233 patients (81.5%) assigned to intraarterial treatment. The adjusted common odds ratio was 1.67 (95% confidence interval [CI], 1.21 to 2.30). There was an absolute difference of 13.5 percentage points (95% CI, 5.9 to 21.2) in the rate of functional independence (modified Rankin score, 0 to 2) in favor of the intervention (32.6% vs. 19.1%). There were no significant differences in mortality or the occurrence of symptomatic intracerebral hemorrhage.
Conclusions: In patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation, intraarterial treatment administered within 6 hours after stroke onset was effective and safe.
(Funded by the Dutch Heart Foundation and others; MR CLEAN Netherlands Trial Registry number, NTR1804, and Current Controlled Trials number, ISRCTN10888758).

Gepubliceerd: N Engl J Med 2015;372(1):11-20
Impact factor: 55.873

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4. CT within 6 hours of headache onset to rule out subarachnoid hemorrhage in nonacademic hospitals
Blok KM, Rinkel GJ, Majoie CB, Hendrikse J, Braaksma M, Tijssen CC, Wong YY, Hofmeijer J, Extercatte J, Kerklaan B, Schreuder TH, ten Holter S, Verheul F,

Harlaar L, Pruissen DM, Kwa VI, Brouwers PJ, Remmers MJ, Schonewille WJ, Kruyt ND, Vergouwen MD

Objective: To investigate whether staff radiologists working in nonacademic hospitals can adequately rule out subarachnoid hemorrhage (SAH) on head CT <6 hours after headache onset.
Methods: In a multicenter, retrospective study, we studied a consecutive series of patients presenting with acute headache to 11 nonacademic hospitals. Inclusion criteria were (1) normal level of consciousness without focal deficits, (2) head CT <6 hours after headache onset and reported negative for the presence of SAH by a staff radiologist, and (3) subsequent CSF spectrophotometry. Two neuroradiologists and one stroke neurologist from 2 academic tertiary care centers independently reviewed admission CTs of patients with CSF results that were considered positive for presence of bilirubin according to local criteria. We investigated the negative predictive value for detection of SAH by staff radiologists in nonacademic hospitals on head CT in patients scanned <6 hours after onset of acute headache.
Results: Of 760 included patients, CSF analysis was considered positive for bilirubin in 52 patients (7%). Independent review of these patients' CTs identified one patient (1/52; 2%) with a perimesencephalic nonaneurysmal SAH. Negative predictive value for detection of subarachnoid blood by staff radiologists working in a nonacademic hospital was 99.9% (95% confidence interval 99.3%-100.0%).
Conclusions: Our results support a change of practice wherein a lumbar puncture can be withheld in patients with a head CT scan performed <6 hours after headache onset and reported negative for the presence of SAH by a staff radiologist in the described nonacademic setting.

Gepubliceerd: Neurology 2015 May 12;84(19):1927-32
Impact factor: 8.185

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5. Poor motor function is associated with reduced sensory processing after stroke
Campfens SF, Zandvliet SB, Meskers CG, Schouten AC, van Putten MJ, van der Kooij H

The possibility to regain motor function after stroke depends on the intactness of motor and sensory pathways. In this study, we evaluated afferent sensory pathway information transfer and processing after stroke with the coherence between cortical activity and a position perturbation (position-cortical coherence, PCC). Eleven subacute stroke survivors participated in this study. Subjects performed a motor task with the affected and non-affected arm while continuous wrist position perturbations were applied. Cortical activity was measured using EEG. PCC was calculated between position perturbation and EEG at the contralateral and ipsilateral sensorimotor area. The presence of PCC was quantified as the number of frequencies where PCC is larger than zero across the sensorimotor area. All subjects showed significant contralateral PCC in affected and non-affected wrist tasks. Subjects with poor motor function had a reduced presence of contralateral PCC compared with subjects with good motor function in the affected wrist tasks.

Amplitude of significant PCC did not differ between subjects with good and poor motor function. Our results show that poor motor function is associated with reduced sensory pathway information transfer and processing in subacute stroke subjects. Position-cortical coherence may provide additional insight into mechanisms of recovery of motor function after stroke.

Gepubliceerd: Exp Brain Res 2015 Apr;233(4):1339-49
Impact factor: 2.036

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6. Stretch Evoked Potentials in Healthy Subjects and After Stroke: A Potential Measure for Proprioceptive Sensorimotor Function
Campfens SF, Meskers CG, Schouten AC, van Putten MJ, van der Kooij H

Sensory feedback is of vital importance in motor control, yet rarely assessed in diseases with impaired motor function like stroke. Muscle stretch evoked potentials (StrEPs) may serve as a measure of cortical sensorimotor activation in response to proprioceptive input. The aim of this study is: 1) to determine early and late features of the StrEP and 2) to explore whether StrEP waveform and features can be measured after stroke. Consistency of StrEP waveforms and features was evaluated in 22 normal subjects. StrEP features and similarity between hemispheres were evaluated in eight subacute stroke subjects. StrEPs of normal subjects had a consistent shape across conditions and sessions (mean cross correlation waveforms > 0.75). Stroke subjects showed heterogeneous StrEP waveforms. Stroke subjects presented a normal early peak (40 ms after movement onset) but later peaks had abnormal amplitudes and latencies. No significant differences between stroke subjects with good and poor motor function were found ($P > 0.14$). With the consistent responses of normal subjects the StrEP meets a prerequisite for potential clinical value. Recording of StrEPs is feasible even in subacute stroke survivors with poor motor function. How StrEP features relate to clinical phenotypes and recovery needs further investigation.

Gepubliceerd: IEEE Trans Neural Syst Rehabil Eng 2015 Jul;23(4):643-54
Impact factor: 3.188

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7. Paracetamol (Acetaminophen) in stroke 2 (PAIS 2): Protocol for a randomized, placebo-controlled, double-blind clinical trial to assess the effect of high-dose paracetamol on functional outcome in patients with acute stroke and a body temperature of 36.5 degrees C or above
de Ridder IR, de Jong FJ, den Hertog HM, Lingsma HF, van Gemert HM, Schreuder AH, Ruitenberg A, Maasland EL, Saxena R, Oomes P, van Tuijl J, Koudstaal PJ, Kappelle LJ, Algra A, van der Worp HB, Dippel DW

Rationale: In the first hours after stroke onset, subfebrile temperatures and fever have been associated with poor functional outcome. In the first Paracetamol (Acetaminophen) in Stroke trial, a randomized clinical trial of 1400 patients with acute stroke, patients who were treated with high-dose paracetamol showed more

improvement on the modified Rankin Scale at three-months than patients treated with placebo, but this difference was not statistically significant. In the 661 patients with a baseline body temperature of 37.0 degrees C or above, treatment with paracetamol increased the odds of functional improvement (odds ratio 1.43; 95% confidence interval: 1.02-1.97). This relation was also found in the patients with a body temperature of 36.5 degrees C or higher (odds ratio 1.31; 95% confidence interval 1.01-1.68). These findings need confirmation.
Aim: The study aims to assess the effect of high-dose paracetamol in patients with acute stroke and a body temperature of 36.5 degrees C or above on functional outcome.
Design: The Paracetamol (Acetaminophen) In Stroke 2 trial is a multicenter, randomized, double-blind, placebo-controlled clinical trial. We use a power of 85% to detect a significant difference in the scores on the modified Rankin Scale of the paracetamol group compared with the placebo group at a level of significance of 0.05 and assume a treatment effect of 7%. Fifteen-hundred patients with acute ischemic stroke or intracerebral hemorrhage and a body temperature of 36.5 degrees C or above will be included within 12 h of symptom onset. Patients will be treated with paracetamol in a daily dose of six-grams or matching placebo for three consecutive days. The Paracetamol (Acetaminophen) In Stroke 2 trial has been registered as NTR2365 in The Netherlands Trial Register.
Study outcomes: The primary outcome will be improvement on the modified Rankin Scale at three-months as analyzed by ordinal logistic regression.
Discussion: If high-dose paracetamol will be proven effective, a simple, safe, and extremely cheap therapy will be available for many patients with acute stroke worldwide.

Gepubliceerd: Int J Stroke 2015;10(3):457-62
Impact factor: 3.833

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8. Safety and feasibiLIty of Metformin in patients with Impaired glucose Tolerance and a recent TIA or minor ischemic stroke (LIMIT) trial - a multicenter, randomized, open-label phase II trial
den Hertog HM, Vermeer SE, Zandbergen AA, Achterberg S, Dippel DW, Algra A, Kappelle LJ, Koudstaal PJ

Background and purpose: We aimed to assess the safety, feasibility, and effects on glucose metabolism of treatment with metformin in patients with TIA or minor ischemic stroke and impaired glucose tolerance.
Methods: We performed a multicenter, randomized, controlled, open-label phase II trial with blinded outcome assessment. Patients with TIA or minor ischemic stroke in the previous six months and impaired glucose tolerance (2-hour post-load glucose levels of 7.8-11.0 mmol/l) were randomized to metformin, in a daily dose of 2 g, or no metformin, for three months. Primary outcome measures were safety and feasibility of metformin, and the adjusted difference in 2-hour post-load glucose levels at three months.
Results: Forty patients were enrolled; 19 patients were randomly assigned metformin. Nine patients in the metformin group had side effects, mostly

gastrointestinal, leading to permanent discontinuation in four patients after 3-10 weeks. Treatment with metformin was associated with a significant reduction in 2-hour post-load glucose levels of 0.97 mmol/l (95% CI 0.11-1.83) in the on-treatment analysis, but not in the intention-to-treat analysis (0.71 mmol/l; 95% CI -0.36 to 1.78).
Conclusions: Treatment with metformin in patients with TIA or minor ischemic stroke and impaired glucose tolerance is safe, but leads to minor side effects. If tolerated, it may lead to a significant reduction in post-load glucose levels. This suggests that the role of metformin as potential therapeutic agent for secondary stroke prevention should be further explored.
Register: This trial is registered as an International Standard Randomized Controlled Trial Number 54960762.

Gepubliceerd: Int J Stroke 2015 Mar 15;10(1):105-9
Impact factor: 3.833

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9. Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial
Fransen PS, Berkhemer OA, Lingsma HF, Beumer D, van den Berg LA, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama ANG, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van Oostenbrugge RJ, Majoie CB, van der Lugt A, Dippel DW

Importance: Intra-arterial treatment (IAT) for acute ischemic stroke caused by intracranial arterial occlusion leads to improved functional outcome in patients treated within 6 hours after onset. The influence of treatment delay on treatment effect is not yet known.
Objective: To evaluate the influence of time from stroke onset to the start of treatment and from stroke onset to reperfusion on the effect of IAT.
Design, Setting, and Participants: The Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) was a multicenter, randomized clinical open-label trial of IAT vs no IAT in 500 patients. The time to the start of treatment was defined as the time from onset of symptoms to groin puncture (TOG). The time from onset of treatment to reperfusion (TOR) was defined as the time to reopening the vessel occlusion or the end of the procedure in cases for which reperfusion was not achieved. Data were collected from December 3, 2010, to June 3, 2014, and analyzed (intention to treat) from July 1, 2014, to September 19, 2015.
Main Outcomes and Measures: Main outcome was the modified Rankin Scale (mRS) score for functional outcome (range, 0 [no symptoms] to 6 [death]). Multiple ordinal logistic regression analysis estimated the effect of treatment and tested for

the interaction of time to randomization, TOG, and TOR with treatment. The effect of treatment as a risk difference on reaching independence (mRS score, 0-2) was computed as a function of TOG and TOR. Calculations were adjusted for age, National Institutes of Health Stroke Scale score, previous stroke, atrial fibrillation, diabetes mellitus, and intracranial arterial terminus occlusion.
Results: Among 500 patients (58% male; median age, 67 years), the median TOG was 260 (interquartile range [IQR], 210-311) minutes; median TOR, 340 (IQR, 274-395) minutes. An interaction between TOR and treatment (P = .04) existed, but not between TOG and treatment (P = .26). The adjusted risk difference (95% CI) was 25.9% (8.3%-44.4%) when reperfusion was reached at 3 hours, 18.8% (6.6%-32.6%) at 4 hours, and 6.7% (0.4%-14.5%) at 6 hours.
Conclusion and Relevance: For every hour of reperfusion delay, the initially large benefit of IAT decreases; the absolute risk difference for a good outcome is reduced by 6% per hour of delay. Patients with acute ischemic stroke require immediate diagnostic workup and IAT in case of intracranial arterial vessel occlusion.
Trial Registration: trialregister.nl Identifier: NTR1804.

Gepubliceerd: JAMA Neurol 2015 Dec 21;1-7
Impact factor: 7.271

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10. CT scans in children with head/brain injury: five years after the revision of the guideline on "mild traumatic head/brain injury"
Hageman G

In 2010 the guideline on mild traumatic head/ brain injury for both adults and children was revised under the supervision of the Dutch Neurology Society. The revised guideline endorsed rules for decisions on whether to carry out diagnostic imaging investigations (brain CT scanning) and formulates indications for admission. Unfortunately, 5 years after its introduction, it is clear that the guideline rules result in excessive brain CT scanning, in which no more serious head injury is diagnosed. Brain injury may be present in (small) children even if symptoms are absent at first presentation. Also, clinical signs do not predict intracranial complications. This was nicely demonstrated in a study by Tilma, Bekhof and Brand of 410 children with mTBI: no clinical symptom or sign reliably predicted the risk of intracranial bleeding. They advise hospitalisation for observation instead of brain CT scanning. It may be necessary to review part of the Dutch guideline on mTBI.

Gepubliceerd: Ned Tijdschr Geneeskd 2015;159:A8759
Impact factor: 0

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11. Early EEG contributes to multimodal outcome prediction of postanoxic coma
Hofmeijer J, Beernink TM, Bosch FH, Beishuizen A, Tjepkema-Cloostermans MC, van Putten MJ

Objectives: Early identification of potential recovery of postanoxic coma is a major challenge. We studied the additional predictive value of EEG.
Methods: Two hundred seventy-seven consecutive comatose patients after cardiac arrest were included in a prospective cohort study on 2 intensive care units. Continuous EEG was measured during the first 3 days. EEGs were classified as unfavorable (isoelectric, low-voltage, burst-suppression with identical bursts), intermediate, or favorable (continuous patterns), at 12, 24, 48, and 72 hours. Outcome was dichotomized as good or poor. Resuscitation, demographic, clinical, somatosensory evoked potential, and EEG measures were related to outcome at 6 months using logistic regression analysis. Analyses of diagnostic accuracy included receiver operating characteristics and calculation of predictive values.
Results: Poor outcome occurred in 149 patients (54%). Single measures unequivocally predicting poor outcome were an unfavorable EEG pattern at 24 hours, absent pupillary light responses at 48 hours, and absent somatosensory evoked potentials at 72 hours. Together, these had a specificity of 100% and a sensitivity of 50%. For the remaining 203 patients, who were still in the "gray zone" at 72 hours, a predictive model including unfavorable EEG patterns at 12 hours, absent or extensor motor response to pain at 72 hours, and higher age had an area under the curve of 0.90 (95% confidence interval 0.84-0.96). Favorable EEG patterns at 12 hours were strongly associated with good outcome. EEG beyond 24 hours had no additional predictive value.
Conclusions: EEG within 24 hours is a robust contributor to prediction of poor or good outcome of comatose patients after cardiac arrest.

Gepubliceerd: Neurology 2015 Jun 12;85(2):137-43
Impact factor: 8.185

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12. Outcome prediction in postanoxic coma with electroencephalography: The sooner the better
Hofmeijer J, Tjepkema-Cloostermans MC, van Putten MJ

Gepubliceerd: Resuscitation 2015 Jun;91:e1-e2
Impact factor: 4.167

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13. Headache in epilepsy patients: the (un)awareness of this phenomenon among Dutch neurologists
Hofstra WA, Hageman G, de Weerd AW

Purpose: Headache is a frequently heard complaint that can strongly influence quality of life. This is probably even more so in people with a chronic illness. Knowing that headache, and especially migraine, is more frequent among epilepsy patients, the knowledge concerning this problem has been studied among Dutch neurologists.
Methods: Seven hundred and seventy two neurologists, working in 89 hospitals and two tertiary epilepsy clinics were asked to participate. Using a questionnaire, neurologists were surveyed on different subjects, e.g. whether they thought current

headaches are more frequent in people with epilepsy than in the general population, their interest for epilepsy and how many patients with epilepsy visited their polyclinic per month.
Results: In total, 334 questionnaires were returned (response rate of 43%) of which 18 were excluded. One third of neurologists responded affirmatively that current headaches are more prevalent among people with epilepsy and eight percent knows that this is, more specified, migraine. The number of years of experience does not influence knowledge on headaches in epilepsy patients. The interest in epilepsy and the number of epilepsy patients per month on the polyclinic does.
Conclusions: These results show that the occurrence of headache in people with epilepsy is underestimated by Dutch neurologists. This leaves an often bothersome and potentially treatable condition underexposed.

Gepubliceerd: Seizure 2015 Feb;25:37-9
Impact factor: 1.822

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14. Periictal and interictal headache including migraine in Dutch patients with epilepsy: a cross-sectional study
Hofstra WA, Hageman G, de Weerd AW

As early as in 1898, it was noted that there was a need to find "a plausible explanation of the long recognized affinities of migraine and epilepsy". However, results of recent studies are clearly conflicting on this matter. In this cross-sectional study, we aimed to define the prevalence and characteristics of both seizure-related and interictal headaches in patients with epilepsy (5-75years) seeking help in the tertiary epilepsy clinic SEIN in Zwolle. Using a questionnaire, subjects were surveyed on the existence of headaches including characteristics, duration, severity, and accompanying symptoms. Furthermore, details on epilepsy were retrieved from medical records (e.g., syndrome, seizure frequency, and use of drugs). Diagnoses of migraine, tension-type headache, or unclassifiable headache were made based on criteria of the International Classification of Headache Disorders. Between March and December 2013, 29 children and 226 adults were evaluated, 73% of whom indicated having current headaches, which is significantly more often when compared with the general population ($p<0.001$). Forty-nine percent indicated having solely interictal headache, while 29% had solely seizure-related headaches and 22% had both. Migraine occurs significantly more often in people with epilepsy in comparison with the general population ($p<0.001$), and the occurrence of tension-type headaches conforms to results in the general population. These results show that current headaches are a significantly more frequent problem amongst people with epilepsy than in people without epilepsy. When comparing migraine prevalence, this is significantly higher in the population of patients with epilepsy.

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Impact factor: 2.257

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15. Time trends in incidence, case fatality, and mortality of intracerebral hemorrhage
Jolink WM, Klijn CJ, Brouwers PJ, Kappelle LJ, Vaartjes I

Objective: To assess age- and sex-specific trends in incidence and 30-day and 1-year case fatality of intracerebral hemorrhage (ICH) in the Netherlands.
Methods: Patients hospitalized for first ICH were identified through linkage of the national hospital discharge register and population register using ICD-9 code 431. We identified out-of-hospital deaths in the national cause of death register. Incidence, 30-day and 1-year case fatality, and total mortality rate were calculated by age and sex. We identified time trends by joinpoint regression analysis and Mann-Kendall tests.
Results: We identified 41,068 cases of ICH (51% men) between 1998 and 2010, of which 6% were out-of-hospital deaths. ICH incidence declined in men and women younger than 75 years (p </= 0.01, not significantly in men 35-54 years) but remained stable in patients 75 years and older. Thirty-day and 1-year case fatality declined in patients younger than 75 years (not significantly in women 35-54 years). In patients aged 35 to 54 years, ICH mortality remained stable until 2003 and then declined slightly (annual percentage change [APC] men: -7.09%; 95% confidence interval [CI] -11.39 to -2.59; women: -8.67%; 95% CI -15.18 to -1.66). In patients 55 to 74 years, mortality declined in men between 1995 and 2010 (APC -4.55%; 95% CI -5.49 to -3.59) and in women between 1992 and 2010 (APC -3.51%; 95% CI -4.16 to -2.85). Mortality did not decline in patients aged 75 years and older.
Conclusion: In the Netherlands, ICH incidence, case fatality, and mortality rates have declined significantly in men and women younger than 75 years but remained stable in patients 75 years and older. The observed time trends may be explained by better prevention and treatment during the previous 2 decades of which the elderly do not seem to benefit.

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Impact factor: 8.185

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16. The effect of vagus nerve stimulation on cardiorespiratory parameters during rest and exercise
Mulders DM, de Vos CC, Vosman I, van Putten MJ

Purpose: Vagus nerve stimulation (VNS) has been successfully applied to reduce seizure frequency in numerous patients with epilepsy. However, various side effects, including dyspnea and bradycardia have been reported, that appear exercise related in some patients. This pilot study aims to obtain insight in the cardiorespiratory effects of VNS during both rest and exercise.
Methods: Patients with a VNS device who experience side effects during exercise are compared with patients without side effects. Respiratory and cardiac parameters measured during rest and exercise include heart rate, breathing frequency and tidal volume.
Results: Sixty-two episodes of VNS in five patients with and five patients without side effects were recorded. In addition, five control subjects have been measured.

During rest, all subjects showed stable values for the cardiorespiratory parameters. During the first minutes of exercise, heart rate, breathing frequency and tidal volume increased. Thereafter, a steady state was reached again for all subjects. During VNS episodes, eight out of 10 patients showed a small but consistent decrease in heart rate, along with an increase in breathing frequency in eight out of nine patients. Tidal volumes decreased during VNS episodes. These effects, induced by VNS, occurred during both rest and exercise. Magnitude of these effects varied between patients, but was not necessarily related to the intensity of the experienced side effects.
Conclusion: This pilot study shows that VNS causes an increase in breathing frequency and a decrease in tidal volume and heart rate in the majority of patients, during both rest and exercise.

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Impact factor: 1.822

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17. Metformin and sitAgliptin in patients with impAired glucose tolerance and a recent TIA or minor ischemic Stroke (MAAS): study protocol for a randomized controlled trial
Osei E, Fonville S, Zandbergen AA, Brouwers PJ, Mulder LJ, Lingsma HF, Dippel DW, Koudstaal PJ, den Hertog HM

Background: Impaired glucose tolerance is present in one third of patients with a TIA or ischemic stroke and is associated with a two-fold risk of recurrent stroke. Metformin improves glucose tolerance, but often leads to side effects. The aim of this study is to explore the feasibility, safety, and effects on glucose metabolism of metformin and sitagliptin in patients with TIA or minor ischemic stroke and impaired glucose tolerance. We will also assess whether a slow increase in metformin dose and better support and information on this treatment will reduce the incidence of side effects in these patients.
Mehtods/Design: The Metformin and sitAgliptin in patients with impAired glucose tolerance and a recent TIA or minor ischemic Stroke trial (MAAS trial) is a phase II, multicenter, randomized, controlled, open-label trial with blinded outcome assessment. Non-diabetic patients (n = 100) with a recent (<6 months) TIA, amaurosis fugax or minor ischemic stroke (modified Rankin scale </= 3) and impaired glucose tolerance, defined as 2-hour post-load glucose levels between 7.8 and 11.0 mmol/L after repeated standard oral glucose tolerance test, will be included. Patients with renal or liver impairment, heart failure, chronic hypoxic lung disease stage III-IV, history of lactate acidosis or diabetic ketoacidosis, pregnancy or breastfeeding, pancreatitis and use of digoxin will be excluded. The patients will be randomly assigned in a 1:1:2 ratio to metformin, sitagliptin or "no treatment." Patients allocated to metformin will start with 500 mg twice daily, which will be slowly increased during a 6-week period to a twice daily dose of 1000 mg. Patients allocated to sitagliptin will be treated with a daily fixed dose of 100 mg. The study has been registered as NTR 3196 in The Netherlands Trial Register. Primary outcomes include percentage still on treatment, percentage of (serious) adverse

events, and the baseline adjusted difference in 2-hour post-load glucose levels at 6 months.
Discussion: This study will give more information about the feasibility and safety of metformin and sitagliptin as well as the effect on 2-hour post-load glucose levels at 6 months in patients with TIA or ischemic stroke and impaired glucose tolerance.
Trial registration number: NTR3196 , Date of registration: 15 December 2011.

Gepubliceerd: Trials 2015;16(1):332
Impact factor: 1.731

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18. Diagnostic yield of external loop recording in patients with acute ischemic stroke or TIA
Plas GJ, Bos J, Oude Velthuis B, Scholten MF, den Hertog HM, Brouwers PJ

Atrial fibrillation (AF) is a strong risk factor for first-ever stroke and stroke recurrence. The detection rate is low and detection is often costly and time-consuming. We evaluated the diagnostic yield of an external loop recorder (ELR) in patients with acute ischemic stroke or TIA, and assessed factors that are associated with AF detection. We prospectively studied patients admitted to the stroke unit with ischemic stroke or TIA, without a history of AF, and no AF on routine-ECG and 24-h telemetry. Patients received an ELR for another 24-h registration. Rhythm registration with an ELR was performed in 94 patients. AF was identified in 5 patients (5 %). AF was associated with cryptogenic stroke and cortical or subcortical involvement. If ELR was limited to patients with cryptogenic stroke in combination with cortical or subcortical involvement, the detection rate increased to 17 %. Automated recording with ELR was easy to use in the acute setting of ischemic stroke or TIA and seems promising to detect AF or atrial flutter, in particular in patients with cryptogenic stroke in combination with cortical or subcortical symptoms.

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Impact factor: 3.377

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19. N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) Levels are Increased in Patients With Transient Ischemic Attack Accompanied by Nonfocal Symptoms
Plas GJ, Jurg SD, Brusse-Keizer M, Dippel DW, Koudstaal PJ, den Hertog HM

Background: Transient nonfocal neurological symptoms may serve as markers of cardiac dysfunction. We assessed whether serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, a biomarker of cardiac disease, are increased in patients with transient ischemic attack (TIA) accompanied by nonfocal symptoms and in patients with attacks of nonfocal symptoms (transient neurological attack [TNA]).
Methods and Results: We included 15 patients with TNA, 69 with TIA accompanied by nonfocal symptoms, 58 with large-vessel TIA, 32 with

cardioembolic TIA, and 46 age- and sex-matched healthy control participants. Serum NT-proBNP levels were determined within 1 week after the attack. We compared log-transformed NT-proBNP levels of patients with cardioembolic TIAs and mixed or nonfocal TNAs, with those of patients with noncardioembolic TIAs as a reference group. Adjustments for age, sex, atrial fibrillation, and a history of nonischemic heart disease were made with a multiple linear regression model. Compared with large-vessel TIA (mean 14.2 pmol/L), mean NT-proBNP levels were significantly higher in patients with TIA accompanied by nonfocal symptoms (40.5 pmol/L, P=0.049) and with cardioembolic TIA (123.5 pmol/L; P=0.004) after adjustments for age, sex, atrial fibrillation, and a history of nonischemic heart disease. Patients with TNA also had higher mean NT-proBNP levels (20.8 pmol/L, P=0.38) than those with large-vessel TIA, but this difference was not statistically significant.
Conclusion: NT-proBNP levels are increased in patients with TIA accompanied by nonfocal symptoms.

Gepubliceerd: J Am Heart Assoc 2015;4(12)4.306
Impact factor: 4.306

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20. Generalized epileptiform discharges in postanoxic encephalopathy: Quantitative characterization in relation to outcome
Ruijter BJ, van Putten MJ, Hofmeijer J

Objective: Electrographic status epilepticus is observed in 10-35% of patients with postanoxic encephalopathy. It remains unclear which electrographic seizure patterns indicate possible recovery, and which are a mere reflection of severe ischemic encephalopathy, where treatment would be futile. We aimed to identify quantitative electroencephalography (EEG) features with prognostic significance.
Methods: From continuous EEG recordings of 47 patients with generalized electrographic status epilepticus after cardiac arrest, 5-min epochs were selected every hour. Epochs were visually assessed and categorized into seven categories, including epileptiform discharges. Five quantitative measures were extracted, reflecting background continuity, discharge frequency, discharge periodicity, relative discharge power, and interdischarge waveform correlation. The best achieved outcome within 6 months after cardiac arrest was categorized as "good" (Cerebral Performance Category 1-2, i.e., no or moderate neurologic disability) or "poor" (CPC 3-5, i.e., severe disability, coma, or death).
Results: Ten patients (22%) had a good outcome. Status epilepticus in patients with good outcome started later (45 vs. 29 h after cardiac arrest, $p < 0.001$), more often ceased for at least 12 h (90% vs. 16%, $p = 0.02$), and was less often treated with antiepileptic drugs (30% vs. 73%, $p = 0.02$). Status epilepticus in patients with a good outcome always evolved from a continuous background pattern, as opposed to evolution from a discontinuous background pattern in 14 patients (38%) with a poor outcome. Epileptiform patterns of patients with good outcome had higher background continuity (1.00 vs. 0.83, $p < 0.001$), higher discharge frequency (1.63 vs. 0.90 Hz, $p = 0.002$), lower relative discharge power (0.29 vs. 0.40, $p = 0.01$), and lower discharge periodicity (0.32 vs. 0.45, $p = 0.04$).

Significance: Our results can be used to identify patients with possible recovery. We speculate that quantitative features associated with poor outcome reflect low neural network complexity, resulting from extensive ischemic damage.

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Impact factor: 4.571

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21. Cardiovascular disease is the main cause of long-term excess mortality after ischemic stroke in young adults
Rutten-Jacobs LC, Arntz RM, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, de Leeuw FE

Adults with stroke at a young age (18-50 years) remain at an increased risk of death for decades. It is unclear what cause underlies this long-term excess mortality and whether this is sex and time specific. Therefore, we investigated sex-specific temporal changes in cause of death after transient ischemic attack or ischemic stroke in young adults aged 18 to 50 years. We included all 845 consecutive 30-day survivors, of a first-ever transient ischemic attack (n=261) or ischemic stroke (n=584), admitted to our hospital between 1980 and 2010. Survival status was assessed at April 1, 2013. Observed cause-specific mortality was compared with expected mortality, derived from mortality rates in the general population with similar age, sex, and calendar-year characteristics. During a median follow-up of 9.2 years, 146 patients (17.3%) died, such that 29 years of life was lost by each individual. For all causes of death, observed mortality exceeded expected mortality. The absolute excess risk of death was for 74% attributable to a vascular cause (absolute excess risk, 2.8 per 1000 person-years [95% confidence interval, 1.8-4.1] for stroke and absolute excess risk, 4.3 per 1000 person-years [95% confidence interval, 2.9-5.9] for other vascular causes). The absolute excess risk was highest between 10 and 15 years after stroke and this peak was most pronounced in men and mainly attributable to vascular death. Long-term excess death after stroke in young adults is mainly attributable to a vascular cause and most pronounced in men. Attempts to reduce the risk of vascular disease after stroke in young adults should extend beyond the acute phase into the long term.

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Impact factor: 6.499

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22. Ipsilateral hippocampal atrophy is associated with long-term memory dysfunction after ischemic stroke in young adults
Schaapsmeerders P, van Uden IW, Tuladhar AM, Maaijwee NA, van Dijk EJ, Rutten-Jacobs LC, Arntz RM, Schoonderwaldt HC, Dorresteijn LD, de Leeuw FE, Kessels RP

Memory impairment after stroke in young adults is poorly understood. In elderly stroke survivors memory impairments and the concomitant loss of hippocampal volume are usually explained by coexisting neurodegenerative disease (e.g.,

amyloid pathology) in interaction with stroke. However, neurodegenerative disease, such as amyloid pathology, is generally absent at young age. Accumulating evidence suggests that infarction itself may cause secondary neurodegeneration in remote areas. Therefore, we investigated the relation between long-term memory performance and hippocampal volume in young patients with first-ever ischemic stroke. We studied all consecutive first-ever ischemic stroke patients, aged 18-50 years, admitted to our academic hospital center between 1980 and 2010. Episodic memory of 173 patients was assessed using the Rey Auditory Verbal Learning Test and the Rey Complex Figure and compared with 87 stroke-free controls. Hippocampal volume was determined using FSL-FIRST, with manual correction. On average 10 years after stroke, patients had smaller ipsilateral hippocampal volumes compared with controls after left-hemispheric stroke (5.4%) and right-hemispheric stroke (7.7%), with most apparent memory dysfunctioning after left-hemispheric stroke. A larger hemispheric stroke was associated with a smaller ipsilateral hippocampal volume (b=-0.003, P<0.0001). Longer follow-up duration was associated with smaller ipsilateral hippocampal volume after left-hemispheric stroke (b=-0.028 ml, P=0.002) and right-hemispheric stroke (b=-0.015 ml, P=0.03). Our results suggest that infarction is associated with remote injury to the hippocampus, which may lower or expedite the threshold for cognitive impairment or even dementia later in life.

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Impact factor: 5.969

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23. Lower Ipsilateral Hippocampal Integrity after Ischemic Stroke in Young Adults: A Long-Term Follow-Up Study

Schaapsmeerders P, Tuladhar AM, Maaijwee NA, Rutten-Jacobs LC, Arntz RM, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, Kessels RP, de Leeuw FE

Background and purpose: Memory impairment after stroke is poorly understood as stroke rarely occurs in the hippocampus. Previous studies have observed smaller ipsilateral hippocampal volumes after stroke compared with controls. Possibly, these findings on macroscopic level are not the first occurrence of structural damage and are preceded by microscopic changes that may already be associated with a worse memory function. We therefore examined the relationship between hippocampal integrity, volume, and memory performance long after first-ever ischemic stroke in young adults.
Methods: We included all consecutive first-ever ischemic stroke patients, without hippocampal strokes or recurrent stroke/TIA, aged 18-50 years, admitted to our academic hospital between 1980 and 2010. One hundred and forty-six patients underwent T1 MPRAGE, DTI scanning and completed the Rey Auditory Verbal Learning Test and were compared with 84 stroke-free controls. After manual correction of hippocampal automatic segmentation, we calculated mean hippocampal fractional anisotropy (FA) and diffusivity (MD).
Results: On average 10 years after ischemic stroke, lesion volume was associated with lower ipsilateral hippocampal integrity (p<0.05), independent of hippocampal volume. In patients with a normal ipsilateral hippocampal volume (volume is less

than or equal to 1.5 SD below the mean volume of controls) significant differences in ipsilateral hippocampal MD were observed ($p<0.0001$). However, patients with a normal hippocampal volume and high hippocampal MD did not show a worse memory performance compared with patients with a normal volume and low hippocampal MD ($p>0.05$).
Conclusions: Patients with average ipsilateral hippocampal volume could already have lower ipsilateral hippocampal integrity, although at present with no attendant worse memory performance compared with patients with high hippocampal integrity. Longitudinal studies are needed to investigate whether a low hippocampal integrity after stroke might lead to exacerbated memory decline with increasing age.

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Impact factor: 3.234

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24. Critical illness-induced dysglycemia and the brain
Sonneville R, Vanhorebeek I, den Hertog HM, Chretien F, Annane D, Sharshar T, Van den Berghe G

Purpose: Dysglycemia is a characteristic feature of critical illness associated with adverse outcome. Whether dysglycemia contributes to brain dysfunction during critical illness and long-term neurological complications is unclear. We give an overview of glucose metabolism in the brain and review the literature on critical illness-induced dysglycemia and the brain.
Methods: Medline database search using relevant search terms on dysglycemia, critical illness, acute brain injury/dysfunction, and randomized controlled trial.
Results: Hyperglycemia has been associated with deleterious effects on the nervous system. Underlying mechanisms in critical illness remain largely speculative and are often extrapolated from knowledge in diabetes mellitus. Increased hyperglycemia-induced blood-brain barrier permeability, oxidative stress, and microglia activation may play a role and compromise neuronal and glial cell integrity. Hypoglycemia is feared as critically ill patients cannot recognize or communicate hypoglycemic symptoms, which furthermore are masked by sedation and analgesia. However, observational data on the impact of brief hypoglycemia on the brain in critical illness are controversial. Secondary analysis of two large randomized studies suggested neuroprotection by strict glycemic control with insulin during intensive care, with lowered intracranial pressure, reduction of seizures, and better long-term rehabilitation in patients with isolated brain injury, and reduced incidence of critical illness polyneuromyopathy in the general critically ill patient population. Several subsequent studies failed to reproduce neurological benefit, likely explained by methodological issues, which include divergent achieved glucose levels and inaccurate glucose monitoring tools.
Conclusions: Preventing hyperglycemia during critical illness holds promise as a neuroprotective strategy to preserve brain cell viability and prevent acute brain dysfunction and long-term cognitive impairment in survivors.

Gepubliceerd: Intensive Care Med 2015;41(2):192-202
Impact factor: 7.214

25. Cognitive performance and poor long-term functional outcome after young stroke
Synhaeve NE, Schaapsmeerders P, Arntz RM, Maaijwee NA, Rutten-Jacobs LC, Schoonderwaldt HC, Dorresteijn LD, de Kort PL, van Dijk EJ, Kessels RP, de Leeuw FE

Objective: To investigate the influence of cognitive performance on long-term functional outcome after ischemic stroke (IS) in young adults aged 18 through 50 years (young IS).
Methods: This study is part of a prospective cohort study among 277 stroke survivors with a young IS admitted to our department between January 1, 1980, and November 1, 2010. Functional outcome was assessed during follow-up between 2009 and 2012 with the modified Rankin Scale (mRS) and Instrumental Activities of Daily Living scale (IADL). Extensive neuropsychological investigation was performed. Logistic regression was used to calculate odds ratios (ORs) for a poor functional outcome (mRS >2 or IADL <8) for the 7 cognitive domains adjudicated for confounders. Cognitive function (continuous) as well as cognitive impairment (dichotomous) were studied.
Results: Only decline in working memory (OR 0.3, 95% confidence interval [CI] 0.1-0.6) was associated with poor functional outcome on the mRS. Except for decline in processing speed (OR 0.5, 95% CI 0.3-0.8) and working memory (OR 0.4, 95% CI 0.2-0.7), no relation was found with poor functional outcome on IADL. Impairment in none of the individual cognitive domains was related to long-term functional outcome, although impairment in global cognitive function was related to a poor functional outcome on the IADL (OR 4.8, 95% CI 1.7-14.0).
Conclusions: On average, 11 years after young IS there was no clear relationship between long-term cognitive deficits and long-term functional outcome or IADL, stressing the need for further prospective studies with further development of sensitive measures of functional prognosis.

Gepubliceerd: Neurology 2015 Sep 1;85(9):776-82
Impact factor: 8.185

26. Masking the Auditory Evoked Potential in TMS-EEG: A Comparison of Various Methods
ter Braack EM, de Vos CC, van Putten MJ

There is growing interest in combining transcranial magnetic stimulation (TMS) with electroencephalography (EEG). Because TMS pulses are accompanied by a clicking sound, it is very likely that part of the response in the EEG consists of an auditory evoked potential (AEP). Different methods have been applied to mask the sound of TMS. However, it is unclear which masking method is most effective in reducing the AEP. In this study we explore the presumed contribution of the AEP to the response and evaluate different ways to mask the TMS clicking sound. Twelve healthy subjects and one completely deaf subject participated in this study. Eight different

masking conditions were evaluated in nine hearing subjects. The amplitude of the N100-P180 complex was compared between the different masking conditions. We were not able to completely suppress the N100-P180 when the coil was placed on top of the head. Using an earmuff or exposing the subjects to white or adapted noise caused a small but significant reduction in N100-P180 amplitude, but the largest reduction was achieved when combining a layer of foam, placed between coil and head, with white or adapted noise. The deaf subject also showed a N100-P180 complex. We conclude that both the TMS clicking sound and cortical activation by the magnetic pulse contribute to the N100-P180 amplitude.

Gepubliceerd: Brain Topogr 2015;28(3):520-8
Impact factor: 3.468

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27. Electroencephalogram Predicts Outcome in Patients With Postanoxic Coma During Mild Therapeutic Hypothermia

Tjepkema-Cloostermans MC, Hofmeijer J, Trof RJ, Blans MJ, Beishuizen A, van Putten MJ

Objective: To assess the value of electroencephalogram for prediction of outcome of comatose patients after cardiac arrest treated with mild therapeutic hypothermia.
Design: Prospective cohort study.
Setting: Medical ICU.
Patients: One hundred forty-two patients with postanoxic encephalopathy after cardiac arrest, who were treated with mild therapeutic hypothermia.
Measurements and main results: Continuous electroencephalogram was recorded during the first 5 days of ICU admission. Visual classification of electroencephalogram patterns was performed in 5-minute epochs at 12 and 24 hours after cardiac arrest by two independent observers, blinded for patients' conditions and outcomes. Patterns were classified as isoelectric, low voltage, epileptiform, burst-suppression, diffusely slowed, or normal. Burst-suppression was subdivided into patterns with and without identical bursts. Primary outcome measure was the neurologic outcome based on each patient's best achieved Cerebral Performance Category score within 6 months after inclusion. 67 patients (47%) had favorable outcome (Cerebral Performance Category, 1-2). In patients with favorable outcome, electroencephalogram patterns improved within 24 hours after cardiac arrest, mostly toward diffusely slowed or normal. At 24 hours after cardiac arrest, the combined group of isoelectric, low voltage, and "burst-suppression with identical bursts" was associated with poor outcome with a sensitivity of 48% (95% CI, 35-61) and a specificity of 100% (95% CI, 94-100). At 12 hours, normal or diffusely slowed electroencephalogram patterns were associated with good outcome with a sensitivity of 56% (95% CI, 41-70) and a specificity of 96% (95% CI, 86-100).
Conclusions: Electroencephalogram allows reliable prediction of both good and poor neurologic outcome of patients with postanoxic encephalopathy treated with mild therapeutic hypothermia within 24 hours after cardiac arrest.

Gepubliceerd: Crit Care Med 2015 Sep 23;43(1):159-67
Impact factor: 6.312

28. The juvenile head trauma syndrome: a trauma triggered migraine?
van der Veek EM, Oosterhoff M, Vos PE, Hageman G

Background: The underlying mechanism of the juvenile head trauma syndrome (JHTS) is still uncertain, but it has been suggested that there is a role in cortical spreading depression, a phenomenon that is assumed to be a part of the pathophysiology of migraine.
Hypothesis: We postulate that children affected by the JHTS are more susceptible to cortical spreading depression, caused by a genetic etiology similar to genetic factors in migraine.
Methods: Children with the JHTS were selected and evaluated retrospectively in an observational case-control study in two Dutch trauma centers in the period between January 2008 and July 2012.
Results: We included 33 patients with the JHTS, who were accounted for approximately 2.5% of the total number (1,342) of children seen at the emergency department with a mild head trauma. The prevalence of migraine in cases compared with controls did not differ. The proportion of patients with a first-degree relative with migraine was significantly higher in cases compared with controls (odds ratio, 2.69; 95% confidence interval, 1.16-6.22; p = 0.010).
Conclusion: The JHTS is a relatively rare phenomenon, seen in approximately 2.5% of all children seen at the emergency department with mild brain injury. This study demonstrates a significant relationship between the JHTS and a positive history of migraine in first-degree relatives.

Gepubliceerd: Neuropediatrics 2015 Apr;46(2):116-22
Impact factor: 1.240

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29. Generalized periodic discharges: Pathophysiology and clinical considerations
van Putten MJ, Hofmeijer J

Generalized periodic discharges (GPDs) are commonly encountered in metabolic encephalopathy and cerebral hypoxia/ischemia. The clinical significance of this EEG pattern is indistinct, and it is unclear whether treatment with antiepileptic drugs is beneficial. In this study, we discuss potential pathophysiological mechanisms. Based on the literature, supplemented with simulations in a minimal computational model, we conclude that selective synaptic failure or neuronal damage of inhibitory interneurons, leading to disinhibition of excitatory pyramidal cells, presumably plays a critical role. Reversibility probably depends on the potential for functional recovery of these interneurons. Whether antiepileptic drugs are helpful for regaining function is unclear. This article is part of a Special Issue entitled "Status Epilepticus".

Gepubliceerd: Epilepsy Behav 2015 Aug;49:228-33
Impact factor: 2.257

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30. Infraslow EEG activity modulates cortical excitability in postanoxic encephalopathy
van Putten MJ, Tjepkema-Cloostermans MC, Hofmeijer J

Infraslow activity represents an important component of physiological and pathological brain function. We study infraslow activity (<0.1 Hz) in 41 patients with postanoxic coma after cardiac arrest, including the relationship between infraslow activity and EEG power in the 3-30 Hz range, using continuous full-band scalp EEG. In all patients, infraslow activity (0.015-0.06 Hz) was present, irrespective of neurological outcome or EEG activity in the conventional frequency bands. In two patients, low-amplitude (10-30 muV) infraslow activity was present while the EEG showed no rhythmic activity above 0.5 Hz. In 13/15 patients with a good outcome and 20/26 patients with a poor one, EEG power in the 3-30 Hz frequency range was correlated with the phase of infraslow activity, quantified by the modulation index. In 9/14 patients with burst-suppression with identical bursts, bursts appeared in clusters, phase-locked to the infraslow oscillations. This is substantiated by a simulation of burst-suppression in a minimal computational model. Infraslow activity is preserved in postanoxic encephalopathy and modulates cortical excitability. The strongest modulation is observed in patients with severe postanoxic encephalopathy and burst-suppression with identical bursts.

Gepubliceerd: J Neurophysiol 2015 May 1;113(9):3256-67
Impact factor: 2.887

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31. Brain damage caused by exposure to organic solvents; diagnostics and disease course of chronic solvent-induced encephalopathy
van Valen E, van Hout MS, Wekking EM, Lenderink AF, van der Laan G, Hageman G

Since 1997 more than 3,000 patients have been referred to one of the two Dutch Solvent Teams with health problems that may have been caused by long-term occupational exposure to organic solvents.- A diagnosis of 'chronic solvent-induced encephalopathy' was made in approximately 500 patients.- The diagnostics of this disease is based on five elements: (a) symptoms in line with the diagnosis; (b) relevant exposure to an organic solvent with neurotoxic effects.

Gepubliceerd: Ned Tijdschr Geneeskd 2015;159:A9431
Impact factor: 0

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32. Magnetic resonance imaging of the carotid artery in long-term head and neck cancer survivors treated with radiotherapy
Wilbers J, Meijer FJ, Kappelle AC, Kaanders JH, Boogerd W, Dorresteijn LD, van Dijk EJ, Steens SC

Background: In head and neck cancer (HNC) patients, long-term treatment-related complications include radiotherapy (RT)-induced carotid vasculopathy and stroke. The current study investigated the magnetic resonance imaging (MRI) characteristics of the carotid wall in long-term HNC survivors treated with RT.
Methods: MRI of the carotid arteries was performed within a prospective cohort of 42 HNC patients on average 7 years after RT. Two independent radiologists assessed maximal vessel wall thickness of common and internal carotid arteries. In case of wall thickening (>/= 2 mm) the MRI signals as well as length of the thickened segment were assessed.
Results: Mean (SD) age of the 42 patients at baseline was 53 (13) years and mean (SD) follow-up time after RT was 6.8 (1.3) years. In total 62% were men and 60% had one or more cerebrovascular risk factors. Mean (SD) dose of RT on the common carotid arteries and internal carotid arteries was 57 Gy (11) and 61 Gy (10), respectively. Wall thickening was observed in 58% of irradiated versus 27% of non-irradiated common carotid arteries and 24% of irradiated versus 6% of non-irradiated internal carotid arteries ($p < 0.05$). Mean (SD) thickness of the irradiated and non-irradiated common carotid arteries was 2.5 (0.9) and 2 (0.7) mm ($p = 0.02$). Mean thickness of the irradiated and non-irradiated internal carotid arteries was 1.8 (0.8) and 1.5 mm (0.3) (n.s.). Mean length of the thickened vessel wall was 48 mm versus 36 mm in the irradiated versus non-irradiated common carotid arteries ($p = 0.03$) and 20 mm versus 15 mm in the irradiated versus non-irradiated internal carotid arteries (n.s.). No significant differences were observed for signal intensities of the vessel walls.
Conclusions: Our study showed significantly more vessel wall thickening in irradiated versus non-irradiated carotid arteries years after RT for HNC, while no differences in signal intensities were observed.

Gepubliceerd: Acta Oncol 2015 Apr 1;1-6
Impact factor: 2.997

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33. How does spreading depression spread? Physiology and modeling
Zandt BJ, Ten Haken B, van Putten MJ, Dahlem MA

Spreading depression (SD) is a wave phenomenon in gray matter tissue. Locally, it is characterized by massive redistribution of ions across cell membranes. As a consequence, there is sustained membrane depolarization and tissue polarization that depress any normal electrical activity. Despite these dramatic events, SD remains difficult to observe in humans noninvasively, which, for long, has slowed advances in this field. The growing appreciation of its clinical importance in migraine and stroke is therefore consistent with an increasing need for computational methods that tackle the complexity of the problem at multiple levels. In this review, we focus on mathematical tools to investigate the question of spread and its two complementary aspects: What are the physiological mechanisms and what is the spatial extent of SD in the cortex? This review discusses two types of models used to study these two questions, namely, Hodgkin-Huxley type and generic activator-inhibitor models, and the recent advances in techniques to link them.

Gepubliceerd: Rev Neurosci 2015;26(2):183-98
Impact factor: 3.330

Totale impact factor: 183.995
Gemiddelde impact factor: 5.576

Aantal artikelen 1e, 2e of laatste auteur: 17
Totale impact factor: 48.402
Gemiddelde impact factor: 2.847

Nucleaire geneeskunde

1. Endocarditis of bovine Contegra valved conduit: a PET-CT spot diagnosis
Mauritz GJ, Wagenaar L, van der Jagt L, Bouman D

Gepubliceerd: Eur Heart J Cardiovasc Imaging 2015 Jun 14;16(10):1173
Impact factor: 4.105

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2. Pre-operative sentinel lymph node localization in breast cancer with superparamagnetic iron oxide MRI: the SentiMAG Multicentre Trial imaging subprotocol
Pouw JJ, Grootendorst MR, Bezooijen R, Klazen CA, De Bruin WI, Klaase JM, Hall-Craggs MA, Douek M, Ten Haken B

Objective: Sentinel lymph node biopsy (SLNB) with a superparamagnetic iron oxide (SPIO) tracer was shown to be non-inferior to the standard combined technique in the SentiMAG Multicentre Trial. The MRI subprotocol of this trial aimed to develop a magnetic alternative for pre-operative lymphoscintigraphy (LS). We evaluated the feasibility of using MRI following the administration of magnetic tracer for pre-operative localization of sentinel lymph nodes (SLNs) and its potential for non-invasive identification of lymph node (LN) metastases.
Methods: Patients with breast cancer scheduled to undergo SLNB were recruited for pre-operative LS, single photon emission CT (SPECT)-CT and SPIO MRI. T1 weighted turbo spin echo and T2 weighted gradient echo sequences were used before and after interstitial injection of magnetic tracer into the breast. SLNs on MRI were defined as LNs with signal drop and direct lymphatic drainage from the injection site. LNs showing inhomogeneous SPIO uptake were classified as metastatic. During surgery, a handheld magnetometer was used for SLNB. Blue or radioactive nodes were also excised. The number of SLNs and MR assessment of metastatic involvement were compared with surgical and histological outcomes.
Results: 11 patients were recruited. SPIO MRI successfully identified SLNs in 10 of 11 patients vs 11 of 11 patients with LS/SPECT-CT. One patient had metastatic involvement of four LNs, and this was identified in one node on pre-operative MRI.
Conclusion: SPIO MRI is a feasible technique for pre-operative localization of SLNs and, in combination with intraoperative use of a handheld magnetometer, provides an entirely radioisotope-free technique for SLNB. Further research is needed for the evaluation of MRI characterization of LN involvement using subcutaneous injection of magnetic tracer.
Advances in knowledge: This study is the first to demonstrate that an interstitially administered magnetic tracer can be used both for pre-operative imaging and intraoperative SLNB, with equal performance to imaging and localization with radioisotopes.

Gepubliceerd: Br J Radiol 2015 Dec;88(1056):20150634
Impact factor: 2.026

Totale impact factor: 6.131
Gemiddelde impact factor: 3.066

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

Orthopedie

1. Pseudotumor formation and serum ions after large head metal-on-metal stemmed total hip replacement. Risk factors, time course and revisions in 706 hips
Bosker BH, Ettema HB, van Rossum M, Boomsma MF, Kollen BJ, Maas M, Verheyen CC

Introduction: The incidence and natural course of pseudotumors in metal-on-metal total hip arthroplasties is largely unknown. The objective of this study was to identify the true incidence and risk factors of pseudotumor formation in large head metal-on-metal total hip arthroplasties.
Materials and Methods: Incidence, time course and risk factors for pseudotumor formation were analysed after large femoral head MoM-THA. We defined a pseudotumor as a (semi-)solid or cystic peri-prosthetic soft-tissue mass with a diameter >/=2 cm that could not be attributed to infection, malignancy, bursa or scar tissue. All patients treated in our clinic with MoM-THA's were contacted. CT scan, metal ions and X-rays were obtained. Symptoms were recorded.
Results: After median follow-up of 3 years, 706 hips were screened in 626 patients. There were 228 pseudotumors (32.3 %) in 219 patients (35.0 %). Pseudotumor formation significantly increased after prolonged follow-up. Seventy-six hips (10.8 %) were revised in 73 patients (11.7 %), independent risk factors were identified. Best cutoff point for cobalt and chromium was 4 mug/l (68 and 77 nmol/l).
Conclusions: This study confirms a high incidence of pseudotumors, dramatically increasing after prolonged follow-up. Risk factors for pseudotumors are of limited importance. Pain was the strongest predictor for pseudotumor presence; cobalt chromium and swelling were considered poor predictors. Cross-sectional imaging is the main screening tool during follow-up.

Gepubliceerd: Arch Orthop Trauma Surg 2015 Mar;135(3):417-25
Impact factor: 1.597

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2. Long-term results of shoulder hemiarthroplasty in patients with rheumatoid arthritis
Geervliet PC, Somford MP, Winia P, van den Bekerom MP

Rheumatoid arthritis affecting the shoulder is typically associated with destruction of the glenohumeral joint and rotator cuff impairment, which can result in severe glenoid erosion. Following hemiarthroplasty, severe glenoid erosion has also frequently been observed. The authors' aim was to retrospectively evaluate the outcome of cemented shoulder hemiarthroplasty in patients with rheumatoid arthritis. The authors performed 45 cemented hemiarthroplasties in 36 patients with rheumatoid arthritis involving the shoulder as well as associated rotator cuff compromise between 1995 and 2008. All patients were analyzed radiologically and clinically using patient-reported outcome measures. Mean+/-SD visual analog pain scale score was 3+/-2. Mean+/-SD Constant score was 55+/-16. Mean+/-SD

validated Dutch version of the Disabilities of the Arm Shoulder and Hand (DASH) score was 42+/-19. No radiograph showed loosening of the implant at follow-up. One patient needed an arthrotomy and capsulotomy because of persistent pain and limited range of motion. Tissue cultures taken during this second operation were negative for infection. No major revision surgery was necessary within the follow-up period. Cemented hemiarthroplasty is a viable treatment option for glenohumeral arthritis in patients with rheumatoid arthritis. Long-term results show acceptable results and low complication rates in this case series for this specific group. A randomized, controlled trial comparing hemiarthroplasty, total shoulder arthroplasty, and reverse shoulder arthroplasty is necessary to draw definite conclusions in this specific patient population.

Gepubliceerd: Orthopedics 2015 Jan;38(1):e38-e42
Impact factor: 0.962

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3. Muller-Weiss disease: idiopathic avascular necrosis of the navicular bone
Goedhart LM, Somford MP, Kempink DR, Zeegers AV

Background: Muller-Weiss disease is a rare and complex foot disorder. The underlying aetiology of this condition involves abnormal loading of the navicular bone combined with delayed ossification. Muller-Weiss disease is progressive and ultimately results in deformation and fragmentation of the navicular bone with plantar-flexed hindfoot varus. In patients with a severe form of this foot deformity, treatment involves arthrodesis of the midfoot with bridging of the navicular bone. **Case description:** A 43-year-old female patient was seen in our outpatient clinic with pain in her right foot. Her symptoms had been present for seven months and had developed spontaneously without prior trauma. Imaging investigations resulted in the diagnosis of Muller-Weiss disease in both her right and her left foot. **Conclusion:** It is important to recognize this condition at an early stage so that patients can receive conservative treatment initially.

Gepubliceerd: Ned Tijdschr Geneeskd 2015;159(0):A9036
Impact factor: 0

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4. Eponyms in elbow fracture surgery
Somford MP, Wiegerinck JI, Hoornenborg D, van den Bekerom MP, Eygendaal D

Eponyms are common in medicine and in orthopaedic surgery. For future reference and historical considerations, we present common eponyms in elbow fracture surgery. We describe in short the biography of the name giver and give, where possible, the original description on which the eponym was based. Whether eponyms should continue to be used is a question that remains unanswered, but if we use them, knowledge of the original description can prevent confusion and knowledge of the historical background sheds light on the interesting roots of our profession.

Gepubliceerd: J Shoulder Elbow Surg 2015 Mar;24(3):369-75
Impact factor: 2.289

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5. Quality of research and quality of reporting in elbow surgery trials
Somford MP, van Deurzen DF, Ostendorf M, Eygendaal D, van den Bekerom MP

Background: Randomized controlled trials (RCTs) are high in the hierarchy of scientific evidence, but possible sources of bias should be identified or even excluded. This systematic review assessed the methodologic quality and the quality of reporting of the RCTs on the treatment of elbow pathology.
Methods: A systematic review of RCTs was performed on the treatment of elbow pathology. PubMed/MEDLINE, Embase, and the Cochrane Library were searched for relevant trials. Thirty-five of the initial 540 articles being an (pseudo) RCT on invasive treatment of elbow pathology in humans were included. These were scored with the use of an adapted Checklists to Evaluate A Report of a Nonpharmacologic Trial (CLEAR-NPT). To assess quality of reporting, points were administered to the articles based on the results from CLEAR-NPT list. The highest possible score for quality is 26 points.
Results: The average quality score was 18.1 points (range, 10-25 points). The mean scores were 19.5 for trials published in the American Journal of Sports Medicine, 19.8 for those published in the Journal of Bone and Joint Surgery, and 20.3 for those published in the Journal of Shoulder and Elbow Surgery.
Conclusions: The most important finding was that the overall quality and the quality of reporting has not improved over the years and that the overall quality of the selected studies and the quality of reporting in these trials is not related to the journal they are published in.

Gepubliceerd: J Shoulder Elbow Surg 2015 Oct;24(10):1619-26
Impact factor: 2.289

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6. Non-steroidal anti-inflammatory drugs (NSAIDs) for treating acute ankle sprains in adults: benefits outweigh adverse events
van den Bekerom MP, Sjer A, Somford MP, Bulstra GH, Struijs PA, Kerkhoffs GM

Purpose: In the recent clinical guideline for acute lateral ankle sprain, the current best evidence for diagnosis, treatment and prevention strategies was evaluated. Key findings for treatment included the use of ice and compression in the initial phase of treatment, in combination with rest and elevation. A short period of taking non-steroidal anti-inflammatory drugs (NSAIDs) may facilitate a rapid decrease in pain and swelling can also be helpful in the acute phase. The objective was to assess the effectiveness and safety of oral and topical NSAID in the treatment for acute ankle sprains.
Methods: Randomised controlled trials comparing oral or topic NSAID treatment with placebo or each other were included. Primary outcome measures were pain at rest or at mobilisation and adverse events. Trials were assessed using the Cochrane risk of bias tool.

Results: Twenty-eight studies were included, and 22 were available for meta-analysis. Superior results were reported for oral NSAIDs when compared with placebo, concerning pain on weight bearing on short term, pain at rest on the short term, and less swelling on short- and intermediate term. For topical NSAIDs, superior results compared with placebo were found for pain at rest (short term), persistent pain (intermediate term), pain on weight bearing (short- and intermediate term) and for swelling (short and intermediate term). No trials were included comparing oral with topic NSAIDs, so conclusions regarding this comparison are not realistic.
Conclusions: The current evidence is limited due to the low number of studies, lack of methodological quality of the included studies as well as the small sample size of the included studies. Nevertheless, the findings from this review support the use of NSAIDs for the initial treatment for acute ankle sprains.

Gepubliceerd: Knee Surg Sports Traumatol Arthrosc 2015;23(8):2390-9
Impact factor: 3.053

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7. Revision of a single type of large metal head metal-on-metal hip prosthesis
van Lingen CP, Ettema HB, Bosker BH, Verheyen CC

Large-head metal-on-metal (MoM) total hip arthroplasties were introduced because of their purported advantages. Inflammatory pseudotumours occasionally occur after MoM hip arthroplasty and often lead to revision. The purpose of this study was to assess the outcome of revision of large-head MoM total hip arthroplasties after an extensive screening protocol for all MoM articulations with a minimum 2 year follow-up. We identified 50 hips that had undergone large-head MoM total hip arthoplasty and required revision at a mean of 44 months after index operation. Of these, 38 were revised for pseudotumours, 7 for loosening, 2 for infection and 3 for instability. There was bone loss in 44 hips. The majority were revised to a 28 mm metal or ceramic head on a polyethylene-cemented cup. In 12 patients there was a complication. There was a decrease of whole blood cobalt from 20.8 microg/L preoperatively to 1.8 microg/L 1 year after revision. We found 6 residual masses on routine postoperative CT scans. The indication for revision of this cohort is inevitable but the clinical outcome 2 years after revision for pseudotumour is disappointing. Revising a MoM hip arthroplasty to a conventional cemented polyethylene or dual-mobility cup with bone impaction grafting and a 28 mm head can adequately treat the high ion levels and probably the disease of ARMD.

Gepubliceerd: Hip Int 2015 May 26;25(3):221-6
Impact factor: 0.756

Totale impact factor: 9.230
Gemiddelde impact factor: 1.319

Aantal artikelen 1e, 2e of laatste auteur: 5
Totale impact factor: 7.137

Gemiddelde impact factor: 1.427

Pathologie

1. The interplay of the Notch signaling in hepatic stellate cells and macrophages determines the fate of liver fibrogenesis
Bansal R, van Baarlen J, Storm G, Prakash J

Hepatic stellate cells (HSCs) known as "master producers" and macrophages as "master regulators", are the key cell types that strongly contribute to the progression of liver fibrosis. Since Notch signaling regulates multiple cellular processes, we aimed to study the role of Notch signaling in HSCs differentiation and macrophages polarization and to evaluate its implication in liver fibrogenesis. Notch pathway components were found to be significantly upregulated in TGFbeta-activated HSCs, inflammatory M1 macrophages, and in mouse and human fibrotic livers. Interestingly, inhibition of Notch using a selective gamma-secretase inhibitor, Avagacestat, significantly inhibited TGFbeta-induced HSC activation and contractility, and suppressed M1 macrophages. Additionally, Avagacestat inhibited M1 driven-fibroblasts activation and fibroblasts-driven M1 polarization (nitric oxide release) in fibroblasts and macrophages co-culture, and conditioned medium studies. In vivo, post-disease treatment with Avagacestat significantly attenuated fibrogenesis in CCl4-induced liver fibrosis mouse model. These effects were attributed to the reduction in HSCs activation, and inhibition of inflammatory M1 macrophages and upregulation of suppressive M2 macrophages. These findings suggest that Notch signaling plays a crucial role in HSC activation and M1/M2 polarization of macrophages in liver fibrosis. These results provide new insights for the development of novel therapies against liver fibrosis through modulation of Notch signaling.

Gepubliceerd: Sci Rep 2015;5:18272
Impact factor: 5.578

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2. Colorectal Liver Metastasis, Primary Gallbladder Carcinoma and Myelofibrosis Present Simultaneously in a Liver Resection Specimen
Gray SA, Raber MH, Provoost E, Toes GJ, Klaase JM

Myelofibrosis and gallbladder carcinoma are both very rare diseases. This case report describes a patient with a history of myelofibrosis and colorectal carcinoma who was diagnosed with colorectal liver metastases. Surgery was performed to remove the metastases, and on site, the gallbladder was removed because of involvement in one of the liver lesions. After pathological examination, a primary gallbladder carcinoma and myelofibrosis were found in addition to the liver metastases. The combination of diseases was not likely to be interconnected but rather an unlucky course of events for the patient.

Gepubliceerd: Case Rep Gastroenterol 2015 Sep;9(3):335-40
Impact factor: 0

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3. Photoacoustic image patterns of breast carcinoma and comparisons with Magnetic Resonance Imaging and vascular stained histopathology
Heijblom M, Piras D, Brinkhuis M, van Hespen JC, van den Engh FM, van der Schaaf M, Klaase JM, van Leeuwen TG, Steenbergen W, Manohar S

Photoacoustic (optoacoustic) imaging can visualize vasculature deep in tissue using the high contrast of hemoglobin to light, with the high-resolution possible with ultrasound detection. Since angiogenesis, one of the hallmarks of cancer, leads to increased vascularity, photoacoustics holds promise in imaging breast cancer as shown in proof-of-principle studies. Here for the first time, we investigate if there are specific photoacoustic appearances of breast malignancies which can be related to the tumor vascularity, using an upgraded research imaging system, the Twente Photoacoustic Mammoscope. In addition to comparisons with x-ray and ultrasound images, in subsets of cases the photoacoustic images were compared with MR images, and with vascular staining in histopathology. We were able to identify lesions in suspect breasts at the expected locations in 28 of 29 cases. We discovered generally three types of photoacoustic appearances reminiscent of contrast enhancement types reported in MR imaging of breast malignancies, and first insights were gained into the relationship with tumor vascularity.

Gepubliceerd: Sci Rep 2015;5:11778
Impact factor: 5.578

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4. Interobserver variation among pathologists for delineation of tumor on H&E-sections of laryngeal and hypopharyngeal carcinoma. How good is the gold standard?
Jager EA, Willems SM, Schakel T, Kooij N, Slootweg PJ, Philippens ME, Caldas-Magalhaes J, Terhaard CH, Raaijmakers CP

Gepubliceerd: Acta Oncol 2015 Jun 13;1-5
Impact factor: 2.997

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5. Bilateral breast cancer, synchronous and metachronous; differences and outcome
Jobsen JJ, van der Palen J, Ong F, Riemersma S, Struikmans H

The aims of this study were twofold: to analyze the incidence of patients having synchronous or metachronous bilateral invasive breast cancer (SBBC and MBBC) and to assess the characteristics and outcome compared to those having unilateral breast cancer (UBC). The used data were obtained from our prospective population-based cohort study which had been started in 1983. Bilateral breast cancer (BBC) was categorized as SBBC (</=3 months of the first primary) or MBBC (>3 months after the first primary). The incidence of SBBC was 1 % and that of MBBC 7.0 %. Patients with UBC showed more ductal carcinoma compared to patients with BBC. MBBC status was an independent significant predictor of local failure (HR 1.9; 95 %

CI 1.3-2.7). SBBC status was an independent predictor of distant metastases (HR 2.6; 95 % CI 1.4-4.5). Overall survival (OS) was better for MBBC (HR 0.6; 95 % CI 0.4-0.8) and worse for SBBC (HR 2.3; 95 % CI 1.5-3.6) compared to UBC. We noted: (1) MBBC showed a significant higher local failure compared to UBC, (2) SBBC, compared to MBBC and UBC had a significant higher distant metastases rate, (3) disease-specific survival and OS were significantly worse for SBBC compared to UBC and MBBC, and (4) that the OS for MBBC compared to UBC, was significantly better.

Gepubliceerd: Breast Cancer Res Treat 2015 Sep;153(2):277-83
Impact factor: 3.940

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6. Long-term effects of first degree family history of breast cancer in young women: Recurrences and bilateral breast cancer
Jobsen JJ, van der Palen J, Brinkhuis M, Ong F, Struikmans H

Background: The aim of this study is to analyze the impact of first degree relative (FDR) of young breast cancer patients.
Methods: Data were used from our prospective population-based cohort study which started in 1983. The family history (FH) was registered with regard to FDR: the presence or absence of invasive breast cancer in none vs. one or more FDRs at any age.
Results: A total of 1109 women, </=50 years with 1128 breast conserving treatments was seen. The incidence of FDR was 17.0% for one FDR and 3.2% >/=2 FDR. The three groups, none, 1 or >/=2 FDR, were comparable. The local failure rate is comparable for all three groups. Women with a positive FH and metachronous bilateral breast cancer (MBBC) showed a lower local failure (HR 0.2; 95% CI 0.05-0.8). A positive FH was an independent predictor for a better disease-specific survival (HR 0.6; 95% CI 0.4-0.9).
Conclusion: A positive FH, based on FDR implies a better prognosis in relation to survival for young women treated with BCT. In contrast to no FH for FDR, MBBC in women with a positive FH was not associated with an increased risk of local recurrence.

Gepubliceerd: Acta Oncol 2015 Sep 23;1-6
Impact factor: 2.997

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7. The prognostic relevance of the mitotic activity index in axillary lymph node-negative breast cancer
Jobsen JJ, van der Palen J, Brinkhuis M, Nortier JW, Struikmans H

The aim of the present study is to look at the mitotic activity index (MAI) as a prognostic factor in a prospective population-based cohort of lymph node-negative invasive breast cancer patients. Analyses were based on 2,048 breast-conserving therapies in 1,971 patients, node-negative, and without any form of adjuvant systemic therapy with long-term follow-up. The 15-year distant metastases-free

survival (DMFS) for women </=55 years was 88.3 % for low MAI values (</=12) versus 73.4 % for high MAI values (>12); (HR 2.8; 95 % CI 1.8-4.4; p < 0.001). Multivariate analyses for DMFS showed significance for MAI. For MAI and Bloom-Richardson grading, by performing a likelihood ratio test, we showed the statistical significance for both. For women >55-years, the MAI was not an independent significant factor. We also confirmed the above findings for disease-specific survival. When multi-gene assays are not available, the MAI remains a robust prognostic marker in women younger than 55 years of age with early node-negative breast cancer.

Gepubliceerd: Breast Cancer Res Treat 2015;149(2):343-51
Impact factor: 3.940

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8. Paediatric nodal marginal zone B-cell lymphadenopathy of the neck: a Haemophilus influenzae-driven immune disorder?

Kluin PM, Langerak AW, Beverdam-Vincent J, Geurts-Giele WR, Visser L, Rutgers B, Schuuring E, van Baarlen J, Lam KH, Seldenrijk K, Kibbelaar RE, de Wit P, Diepstra A, Rosati S, van Noesel MM, Zwaan CM, Hunting JC, Hoogendoorn M, van der Gaag EJ, van Esser JW, de Bont E, Kluin-Nelemans HC, Winter RH, Lo Ten Foe JR, van der Zanden AG

Many hyperplasias and lymphomas of marginal zone B-cells are associated with infection. We identified six children and one adolescent with cervical lymphadenopathy showing prominent polyclonal nodal marginal zone hyperplasia (pNMZH) and four adolescents with monoclonal paediatric nodal marginal zone lymphoma (pNMZL). The clonality status was assessed using BIOMED-2-IG PCR analysis. Haemophilus influenzae was identified in all six cases of pNMZH that could be tested by direct culture (N = 3) or a very sensitive PCR for the H. influenzae gyrase gene in frozen materials (N = 5). H. influenzae was not detected in three pNMZLs and 28 non-specific reactive cervical lymph nodes of age-matched controls, except for a single control node that was obtained during oropharyngeal surgery for a cleft palate showing very low copy numbers of H. influenzae. pNMZH patients were younger than pNMZL patients (median age 12 versus 21 years). pNMZH showed a prominent nodular appearance with variable fibrosis without acute inflammation. Within the nodules, the expanded germinal centres and variably sized marginal zones were colonized by activated B-cells with weak expression of IgD and lack of CD10 and/or BCL6 expression. Some areas showed skewed light chain expression in plasma cells (4/5 cases lambda). In four cases tested, this was confirmed by flow cytometry for surface Ig (3/4 cases lambda). In contrast, pNMZL showed more extensive expansion of marginal zones by centrocytoid cells and often expression of BCL2 protein. Several H. influenzae strains are known to interact with the constant part of IgD on human B-cells, leading to their polyclonal proliferation and activation. We speculate that in vivo stimulation of IgD+ marginal zone B-cells by this bacterium may be implicated in this particular lymphadenopathy that should be distinguished from monoclonal pNMZL.

Gepubliceerd: J Pathol 2015 Jul;236(3):302-14

Impact factor: 7.429

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9. Pathologically confirmed autoimmune encephalitis in suspected Creutzfeldt-Jakob disease
Maat P, de Beukelaar JW, Jansen C, Schuur M, van Duijn CM, van Coevorden MH, de Graaff E, Titulaer M, Rozemuller AJ, Sillevis SP

Objective: To determine the clinical features and presence in CSF of antineuronal antibodies in patients with pathologically proven autoimmune encephalitis derived from a cohort of patients with suspected Creutzfeldt-Jakob disease (CJD).
Methods: The Dutch Surveillance Centre for Prion Diseases performed 384 autopsies on patients with suspected CJD over a 14-year period (1998-2011). Clinical information was collected from treating physicians. Antineuronal antibodies were tested in CSF obtained postmortem by immunohistochemistry on fresh frozen rat brain sections, by Luminex assay for the presence of well-characterized onconeural antibodies, and by cell-based assays for antibodies against NMDAR, GABABR1/2, GABAAR GLUR1/2, LGI1, Caspr2, and DPPX.
Results: In 203 patients, a diagnosis of definite CJD was made, while in 181 a variety of other conditions were diagnosed, mainly neurodegenerative. In 22 of these 181, the neuropathologist diagnosed autoimmune encephalitis. One patient was excluded because of lack of clinical information. Inflammatory infiltrates were predominantly perivascular and consisted mainly of T cells. The predominant locations were basal ganglia and thalamus (90%) and temporal lobes and hippocampus (81%). In 6 patients (29%), antineuronal antibodies were detected in postmortem CSF, directed against Hu, NMDAR, GABABR1/2, Caspr2, and an unidentified synaptic antigen in 2. The most frequent symptoms were dementia (90%), gait disturbance (86%), cerebellar signs (67%), and neuropsychiatric symptoms (67%). Immunopathologic and clinical findings did not differ between autoantibody-negative patients and patients with antineuronal antibodies.
Conclusions: It is important to consider immune-mediated disorders in the differential diagnosis of rapidly progressive neurologic deficits.

Gepubliceerd: Neurol Neuroimmunol Neuroinflamm 2015 Dec;2(6):e178
Impact factor: 0

Totale impact factor: 26.881
Gemiddelde impact factor: 3.360

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 5.578
Gemiddelde impact factor: 5.578

Plastische chirurgie

1. International importance of robust breast device registries
Cooter RD, Barker S, Carroll SM, Evans GR, von Fritschen U, Hoflehner H, Le Louam C, Lumenta DB, Mathijssen IM, McNeil J, Mulgrew S, Mureau MA, Perks G, Rakhorst H, Randquist C, Topaz M, Verheyden C, de Waal J

Background: Breast implants are high-risk devices that have been at the epicenter of much debate and controversy. In light of the Poly Implant Prothese crisis, data registries among 11 national societies around the world are cooperatively calling for the urgent need to establish robust national clinical quality registries based on international best practice within a framework of international collaboration.
Methods: A survey was conducted on the historic and current status of national breast device registries. Eleven countries participated in the study, illustrating different data collection systems and registries around the world. Data collection was designed to illustrate the capabilities of current national registries, with particular focus on capture rate and outcome reporting mechanisms.
Results: A study of national breast implant registries revealed that less than half of the participating countries had operational registries and that none of these had adequately high data capture to enable reliable outcome analysis. The study revealed that the two most common problems that discouraged participation are the complexity of data sets and the opt-in consent model.
Conclusions: Recent implant crises have highlighted the need for robust registries. This article argues the importance of securing at least 90 percent data capture, which is achievable through the opt-out consent model. Since adopting this model, the Australian Breast Device Registry has increased data capture from 4 percent to over 97 percent. Simultaneously, it is important to foster international collaboration from the outset to avoid duplication of efforts and enable the development of effective international early warning systems.

Geplubliceerd: Plast Reconstr Surg 2015 Feb;135(2):330-6
Impact factor: 2.993

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2. Reconstruction of defects involving the Achilles tendon and local soft tissues: a quick solution for a lingering problem
Soons J, Rakhorst HA, Ruettermann M, Luijsterburg AJ, Bos PK, Zöphel OT

A total of seven patients (six men and one woman) with a defect in the Achilles tendon and overlying soft tissue underwent reconstruction using either a composite radial forearm flap (n = 3) or an anterolateral thigh flap (n = 4). The Achilles tendons were reconstructed using chimeric palmaris longus (n = 2) or tensor fascia lata (n = 2) flaps or transfer of the flexor hallucis longus tendon (n = 3). Surgical parameters such as the rate of complications and the time between the initial repair and flap surgery were analysed. Function was measured objectively by recording the circumference of the calf, the isometric strength of the plantar flexors and the range of movement of the ankle. The Achilles tendon Total Rupture Score (ATRS)

questionnaire was used as a patient-reported outcome measure. Most patients had undergone several previous operations to the Achilles tendon prior to flap surgery. The mean time to flap surgery was 14.3 months (2.1 to 40.7). At a mean follow-up of 32.3 months (12.1 to 59.6) the circumference of the calf on the operated lower limb was reduced by a mean of 1.9 cm (sd 0.74) compared with the contralateral limb ($p = 0.042$). The mean strength of the plantar flexors on the operated lower limb was reduced to 88.9% of that of the contralateral limb ($p = 0.043$). There was no significant difference in the range of movement between the two sides ($p = 0.317$). The mean ATRS score was 72 points (sd 20.0). One patient who had an initial successful reconstruction developed a skin defect of the composite flap 12 months after free flap surgery and this resulted in recurrent infections, culminating in transtibial amputation 44 months after reconstruction. These otherwise indicate that reconstruction of the Achilles tendon combined with flap cover results in a successful and functional reconstruction.

Gepubliceerd: Bone Joint J 2015 Feb;97-B(2):215-20
Impact factor: 1.961

Totale impact factor: 4.954
Gemiddelde impact factor: 2.477

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 1.961
Gemiddelde impact factor: 1.961

Psychiatrie

1. Medically unexplained dyspnoea and panic
Hauzer R, Verheul W, Griez E, Wesseling G, van Duinen M

Medically unexplained dyspnoea in the pulmonary setting is often accompanied by considerable levels of anxiety, suggestive of psychopathology, in particular panic disorder (PD). This pilot study investigates the value of the Multidimensional Dyspnea Profile as a tool to facilitate identification of a specific dyspnoea profile suggestive of comorbid PD. The verbal descriptors, feeling depressed, air hunger and concentrating on breathing, significantly differentiated between the two groups of patients with pulmonary disease with and without PD.

Gepubliceerd: Respirology 2015 Jul;20(5):828-30
Impact factor: 3.345

Totale impact factor: 3.345
Gemiddelde impact factor: 3.345

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 3.345
Gemiddelde impact factor: 3.345

Radiologie

1. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke
Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW

Background: In patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion, intraarterial treatment is highly effective for emergency revascularization. However, proof of a beneficial effect on functional outcome is lacking.
Methods: We randomly assigned eligible patients to either intraarterial treatment plus usual care or usual care alone. Eligible patients had a proximal arterial occlusion in the anterior cerebral circulation that was confirmed on vessel imaging and that could be treated intraarterially within 6 hours after symptom onset. The primary outcome was the modified Rankin scale score at 90 days; this categorical scale measures functional outcome, with scores ranging from 0 (no symptoms) to 6 (death). The treatment effect was estimated with ordinal logistic regression as a common odds ratio, adjusted for prespecified prognostic factors. The adjusted common odds ratio measured the likelihood that intraarterial treatment would lead to lower modified Rankin scores, as compared with usual care alone (shift analysis).
Results: We enrolled 500 patients at 16 medical centers in the Netherlands (233 assigned to intraarterial treatment and 267 to usual care alone). The mean age was 65 years (range, 23 to 96), and 445 patients (89.0%) were treated with intravenous alteplase before randomization. Retrievable stents were used in 190 of the 233 patients (81.5%) assigned to intraarterial treatment. The adjusted common odds ratio was 1.67 (95% confidence interval [CI], 1.21 to 2.30). There was an absolute difference of 13.5 percentage points (95% CI, 5.9 to 21.2) in the rate of functional independence (modified Rankin score, 0 to 2) in favor of the intervention (32.6% vs. 19.1%). There were no significant differences in mortality or the occurrence of symptomatic intracerebral hemorrhage.
Conclusions: In patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation, intraarterial treatment administered within 6 hours after stroke onset was effective and safe. (Funded by the Dutch Heart Foundation and others; MR CLEAN Netherlands Trial Registry number, NTR1804 , and Current Controlled Trials number, ISRCTN10888758).

Gepubliceerd: N Engl J Med 2015;372(1):11-20
Impact factor: 55.873

2. A supracondylar process in a child with arm pain
Burfitt-Provoost E, Kichari JR

A 14-year-old boy had arm pain after a traumatic event. An X-ray showed a supracondylar process of the humerus, which is a coincidental finding but sometimes has clinical consequences. It may compress the median nerve or brachial artery, leading to symptoms. Resection can give complete relieve of symptoms.

Gepubliceerd: Ned Tijdschr Geneeskd 2015;159(0):A9028
Impact factor: 0

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3. Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial
Fransen PS, Berkhemer OA, Lingsma HF, Beumer D, van den Berg LA, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama ANG, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van Oostenbrugge RJ, Majoie CB, van der Lugt A, Dippel DW

Importance: Intra-arterial treatment (IAT) for acute ischemic stroke caused by intracranial arterial occlusion leads to improved functional outcome in patients treated within 6 hours after onset. The influence of treatment delay on treatment effect is not yet known.
Objective: To evaluate the influence of time from stroke onset to the start of treatment and from stroke onset to reperfusion on the effect of IAT.
Design, Setting, and Participants: The Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) was a multicenter, randomized clinical open-label trial of IAT vs no IAT in 500 patients. The time to the start of treatment was defined as the time from onset of symptoms to groin puncture (TOG). The time from onset of treatment to reperfusion (TOR) was defined as the time to reopening the vessel occlusion or the end of the procedure in cases for which reperfusion was not achieved. Data were collected from December 3, 2010, to June 3, 2014, and analyzed (intention to treat) from July 1, 2014, to September 19, 2015.
Main Outcomes and Measures: Main outcome was the modified Rankin Scale (mRS) score for functional outcome (range, 0 [no symptoms] to 6 [death]). Multiple ordinal logistic regression analysis estimated the effect of treatment and tested for the interaction of time to randomization, TOG, and TOR with treatment. The effect of treatment as a risk difference on reaching independence (mRS score, 0-2) was computed as a function of TOG and TOR. Calculations were adjusted for age,

National Institutes of Health Stroke Scale score, previous stroke, atrial fibrillation, diabetes mellitus, and intracranial arterial terminus occlusion.
Results: Among 500 patients (58% male; median age, 67 years), the median TOG was 260 (interquartile range [IQR], 210-311) minutes; median TOR, 340 (IQR, 274-395) minutes. An interaction between TOR and treatment (P = .04) existed, but not between TOG and treatment (P = .26). The adjusted risk difference (95% CI) was 25.9% (8.3%-44.4%) when reperfusion was reached at 3 hours, 18.8% (6.6%-32.6%) at 4 hours, and 6.7% (0.4%-14.5%) at 6 hours.
Conclusion and Relevance: For every hour of reperfusion delay, the initially large benefit of IAT decreases; the absolute risk difference for a good outcome is reduced by 6% per hour of delay. Patients with acute ischemic stroke require immediate diagnostic workup and IAT in case of intracranial arterial vessel occlusion.
Trial Registration: trialregister.nl Identifier: NTR1804.

Gepubliceerd: JAMA Neurol 2015 Dec 21;1-7
Impact factor: 7.271

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4. Colorectal Liver Metastasis, Primary Gallbladder Carcinoma and Myelofibrosis Present Simultaneously in a Liver Resection Specimen
Gray SA, Raber MH, Provoost E, Toes GJ, Klaase JM

Myelofibrosis and gallbladder carcinoma are both very rare diseases. This case report describes a patient with a history of myelofibrosis and colorectal carcinoma who was diagnosed with colorectal liver metastases. Surgery was performed to remove the metastases, and on site, the gallbladder was removed because of involvement in one of the liver lesions. After pathological examination, a primary gallbladder carcinoma and myelofibrosis were found in addition to the liver metastases. The combination of diseases was not likely to be interconnected but rather an unlucky course of events for the patient.

Gepubliceerd: Case Rep Gastroenterol 2015 Sep;9(3):335-40
Impact factor: 0

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5. Photoacoustic image patterns of breast carcinoma and comparisons with Magnetic Resonance Imaging and vascular stained histopathology
Heijblom M, Piras D, Brinkhuis M, van Hespen JC, van den Engh FM, van der Schaaf M, Klaase JM, van Leeuwen TG, Steenbergen W, Manohar S

Photoacoustic (optoacoustic) imaging can visualize vasculature deep in tissue using the high contrast of hemoglobin to light, with the high-resolution possible with ultrasound detection. Since angiogenesis, one of the hallmarks of cancer, leads to increased vascularity, photoacoustics holds promise in imaging breast cancer as shown in proof-of-principle studies. Here for the first time, we investigate if there are specific photoacoustic appearances of breast malignancies which can be related to the tumor vascularity, using an upgraded research imaging system, the Twente Photoacoustic Mammoscope. In addition to comparisons with x-ray and ultrasound

images, in subsets of cases the photoacoustic images were compared with MR images, and with vascular staining in histopathology. We were able to identify lesions in suspect breasts at the expected locations in 28 of 29 cases. We discovered generally three types of photoacoustic appearances reminiscent of contrast enhancement types reported in MR imaging of breast malignancies, and first insights were gained into the relationship with tumor vascularity.

Gepubliceerd: Sci Rep 2015;5:11778
Impact factor: 5.578

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6. Long Term Results of Kissing Stents in the Aortic Bifurcation
Hinnen JW, Konickx MA, Meerwaldt R, Kolkert JL, van der Palen J, Huisman AB, Geelkerken RH

Background: To evaluate the long-term outcome after aortoiliac kissing stent placement and to analyze variables, which potentially influence the outcome of endovascular reconstruction of the aortic bifurcation.
Methods: All patients treated with aortoiliac kissing stents at our institution between April 1995 and August 2011 were retrospectively identified from a prospective single-center database. Data regarding patient characteristics (age, gender, smoking, cardio- and cerebrovascular risk factors, hyperlipidaemia, diabetes mellitus and use of antihypertensive medication), symptoms, pre-interventional examination and imaging, procedural details and follow-up were retrieved. Patency rates were calculated with Kaplan-Meier analysis. Factors affecting the patency were determined with Cox uni- and multivariate analysis.
Results: A total of 215 patients (63% men, mean age 61 +/- 10 years) were included. The median follow-up period was 31 (IQR 47.1) months. Primary, primary assisted, and secondary patency rates were 97%, 97%, and 99%, respectively, at one month; 92%, 95% and 94% at four months; 75%, 86%, and 91% at two years; 70%, 81%, and 91% at 5 years; and 67%, 81%, and 91% at ten years. Younger age and previous aortoiliac treatment were predictors for reduced primary and primary assisted patency. Smoking, previous aortoiliac intervention, TASC C and D lesions were predictors for reduced secondary patency.
Conclusions: Reconstruction of the aortoiliac bifurcation with kissing stents is feasible, safe and effective in all types of lesions with satisfying long term patencies. TASC C and D lesions are associated with a higher occlusion rate. Younger age and previous aortoiliac interventions are predictors for reduced primary and primary assisted patency.

Gepubliceerd: Acta Chir Belg 2015 May;115(3):191-7
Impact factor: 0.408

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7. Endocarditis of bovine Contegra valved conduit: a PET-CT spot diagnosis
Mauritz GJ, Wagenaar L, van der Jagt L, Bouman D

Gepubliceerd: Eur Heart J Cardiovasc Imaging 2015 Jun 14;16(10):1173

Impact factor: 4.105

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8. Pre-operative sentinel lymph node localization in breast cancer with superparamagnetic iron oxide MRI: the SentiMAG Multicentre Trial imaging subprotocol
Pouw JJ, Grootendorst MR, Bezooijen R, Klazen CA, De Bruin WI, Klaase JM, Hall-Craggs MA, Douek M, Ten Haken B

Objective: Sentinel lymph node biopsy (SLNB) with a superparamagnetic iron oxide (SPIO) tracer was shown to be non-inferior to the standard combined technique in the SentiMAG Multicentre Trial. The MRI subprotocol of this trial aimed to develop a magnetic alternative for pre-operative lymphoscintigraphy (LS). We evaluated the feasibility of using MRI following the administration of magnetic tracer for pre-operative localization of sentinel lymph nodes (SLNs) and its potential for non-invasive identification of lymph node (LN) metastases.
Methods: Patients with breast cancer scheduled to undergo SLNB were recruited for pre-operative LS, single photon emission CT (SPECT)-CT and SPIO MRI. T1 weighted turbo spin echo and T2 weighted gradient echo sequences were used before and after interstitial injection of magnetic tracer into the breast. SLNs on MRI were defined as LNs with signal drop and direct lymphatic drainage from the injection site. LNs showing inhomogeneous SPIO uptake were classified as metastatic. During surgery, a handheld magnetometer was used for SLNB. Blue or radioactive nodes were also excised. The number of SLNs and MR assessment of metastatic involvement were compared with surgical and histological outcomes.
Results: 11 patients were recruited. SPIO MRI successfully identified SLNs in 10 of 11 patients vs 11 of 11 patients with LS/SPECT-CT. One patient had metastatic involvement of four LNs, and this was identified in one node on pre-operative MRI.
Conclusion: SPIO MRI is a feasible technique for pre-operative localization of SLNs and, in combination with intraoperative use of a handheld magnetometer, provides an entirely radioisotope-free technique for SLNB. Further research is needed for the evaluation of MRI characterization of LN involvement using subcutaneous injection of magnetic tracer.
Advances in knowledge: This study is the first to demonstrate that an interstitially administered magnetic tracer can be used both for pre-operative imaging and intraoperative SLNB, with equal performance to imaging and localization with radioisotopes.

Gepubliceerd: Br J Radiol 2015 Dec;88(1056):20150634
Impact factor: 2.026

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9. Detection and quantification of the solid component in pulmonary subsolid nodules by semiautomatic segmentation
Scholten ET, Jacobs C, van Ginneken B, van Riel S, Vliegenthart R, Oudkerk M, de Koning HJ, Horeweg N, Prokop M, Gietema HA, Mali WP, de Jong PA

Objective: To determine whether semiautomatic volumetric software can differentiate part-solid from nonsolid pulmonary nodules and aid quantification of the solid component.
Methods: As per reference standard, 115 nodules were differentiated into nonsolid and part-solid by two radiologists; disagreements were adjudicated by a third radiologist. The diameters of solid components were measured manually. Semiautomatic volumetric measurements were used to identify and quantify a possible solid component, using different Hounsfield unit (HU) thresholds. The measurements were compared with the reference standard and manual measurements.
Results: The reference standard detected a solid component in 86 nodules. Diagnosis of a solid component by semiautomatic software depended on the threshold chosen. A threshold of -300 HU resulted in the detection of a solid component in 75 nodules with good sensitivity (90%) and specificity (88%). At a threshold of -130 HU, semiautomatic measurements of the diameter of the solid component (mean 2.4 mm, SD 2.7 mm) were comparable to manual measurements at the mediastinal window setting (mean 2.3 mm, SD 2.5 mm [p = 0.63]).
Conclusion: Semiautomatic segmentation of subsolid nodules could diagnose part-solid nodules and quantify the solid component similar to human observers. Performance depends on the attenuation segmentation thresholds. This method may prove useful in managing subsolid nodules. KEY POINTS: * Semiautomatic segmentation can accurately differentiate nonsolid from part-solid pulmonary nodules * Semiautomatic segmentation can quantify the solid component similar to manual measurements * Semiautomatic segmentation may aid management of subsolid nodules following Fleischner Society recommendations * Performance for the segmentation of subsolid nodules depends on the chosen attenuation thresholds.

Gepubliceerd: Eur Radiol 2015 Feb;25(2):488-96
Impact factor: 4.014

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10. Interscan variation of semi-automated volumetry of subsolid pulmonary nodules
Scholten ET, de Jong PA, Jacobs C, van Ginneken B, van Riel S, Willemink MJ, Vliegenthart R, Oudkerk M, de Koning HJ, Horeweg N, Prokop M, Mali WP, Gietema HA

Rationale: We aimed to test the interscan variation of semi-automatic volumetry of subsolid nodules (SSNs), as growth evaluation is important for SSN management.
Methods: From a lung cancer screening trial all SSNs that were stable over at least 3 months were included (N = 44). SSNs were quantified on the baseline CT by two observers using semi-automatic volumetry software for effective diameter, volume, and mass. One observer also measured the SSNs on the second CT 3 months later. Interscan variation was evaluated using Bland-Altman plots. Observer agreement was calculated as intraclass correlation coefficient (ICC). Data are presented as mean (+/- standard deviation) or median and interquartile range (IQR). A Mann-

Whitney U test was used for the analysis of the influence of adjustments on the measurements.
Results: Semi-automatic measurements were feasible in all 44 SSNs. The interscan limits of agreement ranged from -12.0 % to 9.7 % for diameter, -35.4 % to 28.6 % for volume and -27.6 % to 30.8 % for mass. Agreement between observers was good with intraclass correlation coefficients of 0.978, 0.957, and 0.968 for diameter, volume, and mass, respectively.
Conclusion: Our data suggest that when using our software an increase in mass of 30 % can be regarded as significant growth. KEY POINTS: * Recently, recommendations regarding subsolid nodules have stressed the importance of growth quantification. * Volumetric measurement of subsolid nodules is feasible with good interscan agreement. * Increase of mass of 30 % can be regarded as significant growth.

Gepubliceerd: Eur Radiol 2015 Apr;25(4):1040-7
Impact factor: 4.014

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11. Towards a close computed tomography monitoring approach for screen detected subsolid pulmonary nodules?
Scholten ET, de Jong PA, de Hoop B, van Klaveren R, van Amelsvoort-van de Vorst, Oudkerk M, Vliegenthart R, de Koning HJ, van der Aalst CM, Vernhout RM, Groen HJ, Lammers JW, van Ginneken B, Jacobs C, Mali WP, Horeweg N, Weenink C, Thunnissen E, Prokop M, Gietema HA

Pulmonary subsolid nodules (SSNs) have a high likelihood of malignancy, but are often indolent. A conservative treatment approach may therefore be suitable. The aim of the current study was to evaluate whether close follow-up of SSNs with computed tomography may be a safe approach. The study population consisted of participants of the Dutch-Belgian lung cancer screening trial (Nederlands Leuvens Longkanker Screenings Onderzoek; NELSON). All SSNs detected during the trial were included in this analysis. Retrospectively, all persistent SSNs and SSNs that were resected after first detection were segmented using dedicated software, and maximum diameter, volume and mass were measured. Mass doubling time (MDT) was calculated. In total 7135 volunteers were included in the current analysis. 264 (3.3%) SSNs in 234 participants were detected during the trial. 147 (63%) of these SSNs in 126 participants disappeared at follow-up, leaving 117 persistent or directly resected SSNs in 108 (1.5%) participants available for analysis. The median follow-up time was 95 months (range 20-110 months). 33 (28%) SSNs were resected and 28 of those were (pre-) invasive. None of the non-resected SSNs progressed into a clinically relevant malignancy. Persistent SSNs rarely developed into clinically manifest malignancies unexpectedly. Close follow-up with computed tomography may be a safe option to monitor changes.

Gepubliceerd: Eur Respir J 2015 Mar;45(3):765-73
Impact factor: 7.636

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12. The Preoperative CT-Scan Can Help to Predict Postoperative Complications after Pancreatoduodenectomy
Schroder FF, de Graaff F, Bouman DE, Brusse-Keizer M, Slump KH, Klaase JM

After pancreatoduodenectomy, complication rates are up to 40%. To predict the risk of developing postoperative pancreatic fistula or severe complications, various factors were evaluated. 110 consecutive patients undergoing pancreatoduodenectomy at our institute between January 2012 and September 2014 with complete CT scan were retrospectively identified. Pre-, per-, and postoperative patients and pathological information were gathered. The CT-scans were analysed for the diameter of the pancreatic duct, attenuation of the pancreas, and the visceral fat area. All data was statistically analysed for predicting POPF and severe complications by univariate and multivariate logistic regression analyses. The POPF rate was 18%. The VFA measured at umbilicus (OR 1.01; 95% CI = 1.00-1.02; P = 0.011) was an independent predictor for POPF. The severe complications rate was 33%. Independent predictors were BMI (OR 1.24; 95% CI = 1.10-1.42; P = 0.001), ASA class III (OR 17.10; 95% CI = 1.60-182.88; P = 0.019), and mean HU (OR 0.98; 95% CI = 0.96-1.00; P = 0.024). In conclusion, VFA measured at the umbilicus seems to be the best predictor for POPF. BMI, ASA III, and the mean HU of the pancreatic body are independent predictors for severe complications following PD.

Gepubliceerd: Biomed Res Int 2015;2015:824525
Impact factor: 1.579

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13. Reproducibility of Volumetric Computed Tomography of Stable Small Pulmonary Nodules with Implications on Estimated Growth Rate and Optimal Scan Interval
Smith GT, Rahman AR, Li M, Moore B, Gietema H, Veronesi G, Massion PP, Walker RC

Purpose: To use clinically measured reproducibility of volumetric CT (vCT) of lung nodules to estimate error in nodule growth rate in order to determine optimal scan interval for patient follow-up.
Methods: We performed quantitative vCT on 89 stable non-calcified nodules and 49 calcified nodules measuring 3-13 mm diameter in 71 patients who underwent 3-9 repeat vCT studies for clinical evaluation of pulmonary nodules. Calculated volume standard deviation as a function of mean nodule volume was used to compute error in estimated growth rate. This error was then used to determine the optimal patient follow-up scan interval while fixing the false positive rate at 5%.
Results: Linear regression of nodule volume standard deviation versus the mean nodule volume for stable non-calcified nodules yielded a slope of 0.057+/-0.002 ($r^2 = 0.79$, $p<0.001$). For calcified stable nodules, the regression slope was 0.052+/-0.005 ($r^2 = 0.65$, $p = 0.03$). Using this with the error propagation formula, the optimal patient follow-up scan interval was calculated to be 81 days, independent of initial nodule volume.

Conclusions: Reproducibility of vCT is excellent, and the standard error is proportional to the mean calculated nodule volume for the range of nodules examined. This relationship constrains statistical certainty of vCT calculated doubling times and results in an optimal scan interval that is independent of the initial nodule volume.

Gepubliceerd: PLoS One 2015;10(9):e0138144
Impact factor: 3.234

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14. Mandatory imaging cuts costs and reduces the rate of unnecessary surgeries in the diagnostic work-up of patients suspected of having appendicitis.
Lahaye MJ, Lambregts DM, Mutsaers E, Essers BA, Breukink S, Cappendijk VC, Beets GL, Beets-Tan RG

Objective: To evaluate whether mandatory imaging is an effective strategy in suspected appendicitis for reducing unnecessary surgery and costs.
Methods: In 2010, guidelines were implemented in The Netherlands recommending the mandatory use of preoperative imaging to confirm/refute clinically suspected appendicitis. This retrospective study included 1,556 consecutive patients with clinically suspected appendicitis in 2008-2009 (756 patients/group I) and 2011-2012 (800 patients/group II). Imaging use (none/US/CT and/or MRI) was recorded. Additional parameters were: complications, medical costs, surgical and histopathological findings. The primary study endpoint was the number of unnecessary surgeries before and after guideline implementation.
Results: After clinical examination by a surgeon, 509/756 patients in group I and 540/800 patients in group II were still suspected of having appendicitis. In group I, 58.5% received preoperative imaging (42% US/12.8% CT/3.7% both), compared with 98.7% after the guidelines (61.6% US/4.4% CT/ 32.6% both). The percentage of unnecessary surgeries before the guidelines was 22.9%. After implementation, it dropped significantly to 6.2% ($p<0.001$). The surgical complication rate dropped from 19.9% to 14.2%. The average cost-per-patient decreased by 594 <euro> from 2,482 to 1,888 <euro> (CL:-1081; -143).
Conclusion: Increased use of imaging in the diagnostic work-up of patients with clinically suspected appendicitis reduced the rate of negative appendectomies, surgical complications and costs.

Gepubliceerd: Eur Radiol. 2015 May;25(5):1464-70
Impact factor: 4.014

Totale impact factor: 99.344
Gemiddelde impact factor: 7.096

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 15.755
Gemiddelde impact factor: 3.939

Radiotherapie

1. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer - A pooled analysis of PORTEC 1 and 2 trials

Bosse T, Peters EE, Creutzberg CL, Jurgenliemk-Schulz IM, Jobsen JJ, Mens JW, Lutgens LC, van der Steen-Banasik EM, Smit VT, Nout RA

Background: Lymph-vascular space invasion (LVSI) is an important adverse prognostic factor in endometrial cancer (EC). However, its role in relation to type of recurrence and adjuvant treatment is not well defined, and there is significant interobserver variation. This study aimed to quantify LVSI and correlate this to risk and type of recurrence.
Methods: In the post operative radiation therapy in endometrial carcinoma (PORTEC)-trials stage I EC patients were randomised to receive external beam radiotherapy (EBRT) versus no additional treatment after surgery (PORTEC-1, n=714), or to EBRT versus vaginal brachytherapy (PORTEC-2, n=427). In tumour samples of 926 (81.2%) patients with endometrioid tumours LVSI was quantified using 2-, 3- and 4-tiered scoring systems. Cox proportional hazard models were used for time-to-event analysis.
Results: Any degree of LVSI was identified in 129 cases (13.9%). Substantial LVSI (n=44, 4.8%) using the 3-tiered approach had the strongest impact on the risk of distant metastasis (hazard ratio (HR) 4.5 confidence interval (CI) 2.4-8.5). In multivariate analysis (including: age, depth of myometrial invasion, grade, treatment) substantial LVSI remained the strongest independent prognostic factor for pelvic regional recurrence (HR 6.2 CI 2.4-16), distant metastasis (HR 3.6 CI 1.9-6.8) and overall survival (HR 2.0 CI 1.3-3.1). Only EBRT (HR 0.3 CI 0.1-0.8) reduced the risk of pelvic regional recurrence.
Conclusions: Substantial LVSI, in contrast to focal or no LVSI, was the strongest independent prognostic factor for pelvic regional recurrence, distant metastasis and overall survival. Therapeutic decisions should be based on the presence of substantial, not 'any' LVSI. Adjuvant EBRT and/or chemotherapy should be considered for stage I EC with substantial LVSI.

Gepubliceerd: Eur J Cancer 2015 Sep;51(13):1742-50
Impact factor: 5.417

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2. Prognostic Significance of POLE Proofreading Mutations in Endometrial Cancer

Church DN, Stelloo E, Nout RA, Valtcheva N, Depreeuw J, Ter Haar N, Noske A, Amant F, Tomlinson IP, Wild PJ, Lambrechts D, Jurgenliemk-Schulz IM, Jobsen JJ, Smit VT, Creutzberg CL, Bosse T

Background: Current risk stratification in endometrial cancer (EC) results in frequent over- and underuse of adjuvant therapy, and may be improved by novel

biomarkers. We examined whether POLE proofreading mutations, recently reported in about 7% of ECs, predict prognosis.
Methods: We performed targeted POLE sequencing in ECs from the PORTEC-1 and -2 trials (n = 788), and analyzed clinical outcome according to POLE status. We combined these results with those from three additional series (n = 628) by meta-analysis to generate multivariable-adjusted, pooled hazard ratios (HRs) for recurrence-free survival (RFS) and cancer-specific survival (CSS) of POLE-mutant ECs. All statistical tests were two-sided.
Results: POLE mutations were detected in 48 of 788 (6.1%) ECs from PORTEC-1 and-2 and were associated with high tumor grade (P < .001). Women with POLE-mutant ECs had fewer recurrences (6.2% vs 14.1%) and EC deaths (2.3% vs 9.7%), though, in the total PORTEC cohort, differences in RFS and CSS were not statistically significant (multivariable-adjusted HR = 0.43, 95% CI = 0.13 to 1.37, P = .15; HR = 0.19, 95% CI = 0.03 to 1.44, P = .11 respectively). However, of 109 grade 3 tumors, 0 of 15 POLE-mutant ECs recurred, compared with 29 of 94 (30.9%) POLE wild-type cancers; reflected in statistically significantly greater RFS (multivariable-adjusted HR = 0.11, 95% CI = 0.001 to 0.84, P = .03). In the additional series, there were no EC-related events in any of 33 POLE-mutant ECs, resulting in a multivariable-adjusted, pooled HR of 0.33 for RFS (95% CI = 0.12 to 0.91, P = .03) and 0.26 for CSS (95% CI = 0.06 to 1.08, P = .06).
Conclusion: POLE proofreading mutations predict favorable EC prognosis, independently of other clinicopathological variables, with the greatest effect seen in high-grade tumors. This novel biomarker may help to reduce overtreatment in EC.

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Impact factor: 12.583

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3. Nomograms for prediction of outcome with or without adjuvant radiation therapy for patients with endometrial cancer: a pooled analysis of PORTEC-1 and PORTEC-2 trials
Creutzberg CL, van Stiphout RG, Nout RA, Lutgens LC, Jurgenliemk-Schulz IM, Jobsen JJ, Smit VT, Lambin P

Background: Postoperative radiation therapy for stage I endometrial cancer improves locoregional control but is without survival benefit. To facilitate treatment decision support for individual patients, accurate statistical models to predict locoregional relapse (LRR), distant relapse (DR), overall survival (OS), and disease-free survival (DFS) are required.
Methods and Materials: Clinical trial data from the randomized Post Operative Radiation Therapy for Endometrial Cancer (PORTEC-1; N=714 patients) and PORTEC-2 (N=427 patients) trials and registered group (grade 3 and deep invasion, n=99) were pooled for analysis (N=1240). For most patients (86%) pathology review data were available; otherwise original pathology data were used. Trial variables which were clinically relevant and eligible according to data constraints were age, stage, given treatment (pelvic external beam radiation therapy (EBRT), vaginal brachytherapy (VBT), or no adjuvant treatment, FIGO histological grade, depth of invasion, and lymph-vascular invasion (LVSI). Multivariate analyses were based on

Cox proportional hazards regression model. Predictors were selected based on a backward elimination scheme. Model results were expressed by the c-index (0.5-1.0; random to perfect prediction). Two validation sets (n=244 and 291 patients) were used.
Results: Accuracy of the developed models was good, with training accuracies between 0.71 and 0.78. The nomograms validated well for DR (0.73), DFS (0.69), and OS (0.70), but validation was only fair for LRR (0.59). Ranking of variables as to their predictive power showed that age, tumor grade, and LVSI were highly predictive for all outcomes, and given treatment for LRR and DFS. The nomograms were able to significantly distinguish low- from high-probability patients for these outcomes.
Conclusions: The nomograms are internally validated and able to accurately predict long-term outcome for endometrial cancer patients with observation, pelvic EBRT, or VBT after surgery. These models facilitate decision support in daily clinical practice and can be used for patient counseling and shared decision making, selecting patients who benefit most from adjuvant treatment, and generating new hypotheses.

Gepubliceerd: Int J Radiat Oncol Biol Phys 2015 Mar 1;91(3):530-9
Impact factor: 4.258

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4. Long-Term Impact of Endometrial Cancer Diagnosis and Treatment on Health-Related Quality of Life and Cancer Survivorship: Results From the Randomized PORTEC-2 Trial
de Boer SM, Nout RA, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, van der Steen-Banasik EM, Mens JW, Slot A, Stenfert Kroese MC, Oerlemans S, Putter H, Verhoeven-Adema KW, Nijman HW, Creutzberg CL

Purpose: To evaluate the long-term health-related quality of life (HRQL) after external beam radiation therapy (EBRT) or vaginal brachytherapy (VBT) among PORTEC-2 trial patients, evaluate long-term bowel and bladder symptoms, and assess the impact of cancer on these endometrial cancer (EC) survivors.
Patients and Methods: In the PORTEC-2 trial, 427 patients with stage I high-intermediate-risk EC were randomly allocated to EBRT or VBT. The 7- and 10-year HRQL questionnaires consisted of EORTC QLQ-C30; subscales for bowel and bladder symptoms; the Impact of Cancer Questionnaire; and 14 questions on comorbidities, walking aids, and incontinence pads. Analysis was done using linear mixed models for subscales and (ordinal) logistic regression with random effects for single items. A two-sided P value <.01 was considered statistically significant.
Results: Longitudinal HRQL analysis showed persisting higher rates of bowel symptoms with EBRT, without significant differences in global health or any of the functioning scales. At 7 years, clinically relevant fecal leakage was reported by 10.6% in the EBRT group, versus 1.8% for VBT (P=.03), diarrhea by 8.4% versus 0.9% (P=.04), limitations due to bowel symptoms by 10.5% versus 1.8% (P=.001), and bowel urgency by 23.3% versus 6.6% (P<.001). Urinary urgency was reported by 39.3% of EBRT patients, 25.5% for VBT, P=.05. No difference in sexual activity

was seen between treatment arms. Long-term impact of cancer scores was higher among the patients who had an EC recurrence or second cancer.
Conclusions: More than 7 years after treatment, EBRT patients reported more bowel symptoms with impact on daily activities, and a trend for more urinary symptoms, without impact on overall quality of life or difference in cancer survivorship issues.

Gepubliceerd: Int J Radiat Oncol Biol Phys 2015 Nov 15;93(4):797-809
Impact factor: 4.258

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5. Bilateral breast cancer, synchronous and metachronous; differences and outcome
Jobsen JJ, van der Palen J, Ong F, Riemersma S, Struikmans H

The aims of this study were twofold: to analyze the incidence of patients having synchronous or metachronous bilateral invasive breast cancer (SBBC and MBBC) and to assess the characteristics and outcome compared to those having unilateral breast cancer (UBC). The used data were obtained from our prospective population-based cohort study which had been started in 1983. Bilateral breast cancer (BBC) was categorized as SBBC (</=3 months of the first primary) or MBBC (>3 months after the first primary). The incidence of SBBC was 1 % and that of MBBC 7.0 %. Patients with UBC showed more ductal carcinoma compared to patients with BBC. MBBC status was an independent significant predictor of local failure (HR 1.9; 95 % CI 1.3-2.7). SBBC status was an independent predictor of distant metastases (HR 2.6; 95 % CI 1.4-4.5). Overall survival (OS) was better for MBBC (HR 0.6; 95 % CI 0.4-0.8) and worse for SBBC (HR 2.3; 95 % CI 1.5-3.6) compared to UBC. We noted: (1) MBBC showed a significant higher local failure compared to UBC, (2) SBBC, compared to MBBC and UBC had a significant higher distant metastases rate, (3) disease-specific survival and OS were significantly worse for SBBC compared to UBC and MBBC, and (4) that the OS for MBBC compared to UBC, was significantly better.

Gepubliceerd: Breast Cancer Res Treat 2015 Sep;153(2):277-83
Impact factor: 3.940

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6. Long-term effects of first degree family history of breast cancer in young women: Recurrences and bilateral breast cancer
Jobsen JJ, van der Palen J, Brinkhuis M, Ong F, Struikmans H

Background: The aim of this study is to analyze the impact of first degree relative (FDR) of young breast cancer patients.
Methods: Data were used from our prospective population-based cohort study which started in 1983. The family history (FH) was registered with regard to FDR: the presence or absence of invasive breast cancer in none vs. one or more FDRs at any age.

Results: A total of 1109 women, </=50 years with 1128 breast conserving treatments was seen. The incidence of FDR was 17.0% for one FDR and 3.2% >/=2 FDR. The three groups, none, 1 or >/=2 FDR, were comparable. The local failure rate is comparable for all three groups. Women with a positive FH and metachronous bilateral breast cancer (MBBC) showed a lower local failure (HR 0.2; 95% CI 0.05-0.8). A positive FH was an independent predictor for a better disease-specific survival (HR 0.6; 95% CI 0.4-0.9).
Conclusion: A positive FH, based on FDR implies a better prognosis in relation to survival for young women treated with BCT. In contrast to no FH for FDR, MBBC in women with a positive FH was not associated with an increased risk of local recurrence.

Gepubliceerd: Acta Oncol 2015 Sep 23;1-6
Impact factor: 2.997

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7. The prognostic relevance of the mitotic activity index in axillary lymph node-negative breast cancer
Jobsen JJ, van der Palen J, Brinkhuis M, Nortier JW, Struikmans H

The aim of the present study is to look at the mitotic activity index (MAI) as a prognostic factor in a prospective population-based cohort of lymph node-negative invasive breast cancer patients. Analyses were based on 2,048 breast-conserving therapies in 1,971 patients, node-negative, and without any form of adjuvant systemic therapy with long-term follow-up. The 15-year distant metastases-free survival (DMFS) for women </=55 years was 88.3 % for low MAI values (</=12) versus 73.4 % for high MAI values (>12); (HR 2.8; 95 % CI 1.8-4.4; p < 0.001). Multivariate analyses for DMFS showed significance for MAI. For MAI and Bloom-Richardson grading, by performing a likelihood ratio test, we showed the statistical significance for both. For women >55-years, the MAI was not an independent significant factor. We also confirmed the above findings for disease-specific survival. When multi-gene assays are not available, the MAI remains a robust prognostic marker in women younger than 55 years of age with early node-negative breast cancer.

Gepubliceerd: Breast Cancer Res Treat 2015;149(2):343-51
Impact factor: 3.940

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8. Factors influencing time between surgery and radiotherapy: A population based study of breast cancer patients
Katik S, Gort M, Jobsen JJ, Maduro JH, Struikmans H, Siesling S

This study describes variation in the time interval between surgery and radiotherapy in breast cancer (BC) patients and assesses factors at patient, hospital and radiotherapy centre (RTC) level influencing this variation. To do so, the factors were investigated in BC patients using multilevel logistic regression. The study sample consisted of 15,961 patients from the Netherlands Cancer Registry at 79 hospitals

and 19 (RTCs) with breast-conserving surgery or mastectomy directly followed by radiotherapy. The percentage of patients starting radiotherapy </=42 days varied from 14% to 94%. Early year of incidence, higher age, higher stage, mastectomy, higher ASA category and no availability of radiotherapy facilities were significantly associated with a longer time interval between radiotherapy and surgery. More patients received radiotherapy </=42 days in hospitals with on-site radiotherapy facilities (OR 1.36, p = 0.024). Among the remainder, significant variation was found at the RTC level (11.1%, sigma(2) = 0.254, SE 0.054), and at the hospital level (6.4% sigma2 = 0.443, SE 0.163) (ICC 0.064). The significant delay and unexplained variance remaining at the RCT and hospital level suggests delays caused by the patient referral pathway from hospital to RCT, and indicates potential for improvement at both levels.

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Impact factor: 2.381

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9. A 43-Year-Old Female with Multifocal Cerebral Lesions. Histiocytic Sarcoma
Nieuwenhuis MB, van der Salm SM, Verhoeff JJ, van der Kooi AJ, Slavujecvic-Letic I, Pals ST, Vos JM

Gepubliceerd: Brain Pathol 2015 May;25(3):371-2
Impact factor: 4.643

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10. Bevacizumab in combination with radiotherapy and temozolomide for patients with newly diagnosed glioblastoma multiforme
van Linde ME, Verhoeff JJ, Richel DJ, van Furth WR, Reijneveld JC, Verheul HM, Stalpers LJ

Background: Patients with a newly diagnosed glioblastoma multiforme (GBM) have a high risk of recurrent disease with a dismal outcome despite intensive treatment of sequential surgery and chemoradiotherapy with temozolomide (TMZ), followed by TMZ as a single agent. Bevacizumab (BV) may increase response rates to chemotherapy in the recurrent treatment setting of GBM. We hypothesized that a neoadjuvant treatment strategy for patients with newly diagnosed GBM using chemoradiotherapy plus BV would improve resectability and thus survival. We performed a phase II trial of the treatment strategy of BV plus chemoradiation to determine the safety of this combination in patients who had already undergone primary surgery for their GBM.
Methods: After a biopsy (6 patients) or a resection (13 patients) of a newly diagnosed GBM, 19 patients received radiotherapy (30 fractions of 2 Gy) in combination with daily TMZ 75 mg/m(2) and BV 10 mg/kg on days 1, 14, and 28, followed by 6 monthly cycles of TMZ 150-200 mg/m(2) on days 1-5.
Results: The overall response rate was 26%. Three patients had a complete response after resection, and in two patients, a complete response after resection followed by chemoradiation plus BV was seen. No grade 3-4 toxicities were observed during combination treatment. The median progression-free survival was

9.6 months (95% confidence interval [CI]: 4.3-14.4 months). The median overall survival was 16 months (95% CI: 8.1-26.3 months), similar to a matched control group that received standard chemoradiotherapy from our institution.
Conclusion: Combination of bevacizumab with radiotherapy and TMZ is safe and feasible in patients with newly diagnosed GBM, but because of low response rates, this treatment strategy does not favor a neoadjuvant approach.

Gepubliceerd: Oncologist 2015 Feb;20(2):107-8
Impact factor: 4.865

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11. Quality of Life in Relation to Pain Response to Radiation Therapy for Painful Bone Metastases
Westhoff PG, de Graeff A, Monninkhof EM, Pomp J, van Vulpen M, Leer JW, Marijnen CA, van der Linden YM

Purpose: To study quality of life (QoL) in responders and nonresponders after radiation therapy for painful bone metastases; and to identify factors predictive for a pain response.
Patients and Methods: The prospectively collected data of 956 patients with breast, prostate, and lung cancer within the Dutch Bone Metastasis Study were used. These patients, irradiated for painful bone metastases, rated pain, QoL, and overall health at baseline and weekly afterward for 12 weeks. Using generalized estimating equations analysis, the course of QoL was studied, adjusted for primary tumor. To identify predictive variables, proportional hazard analyses were performed, taking into account death as a competing risk, and C-statistics were calculated for discriminative value.
Results: In total, 722 patients (76%) responded to radiation therapy. During follow-up, responders had a better QoL in all domains compared with nonresponders. Patients with breast or prostate cancer had a better QoL than patients with lung cancer. In multivariate analysis, baseline predictors for a pain response were breast or prostate cancer as primary tumor, younger age, good performance status, absence of visceral metastases, and using opioids. The discriminative ability of the model was low (C-statistic: 0.56).
Conclusions: Responding patients show a better QoL after radiation therapy for painful bone metastases than nonresponders. Our model did not have enough discriminative power to predict which patients are likely to respond to radiation therapy. Therefore, radiation therapy should be offered to all patients with painful bone metastases, aiming to decrease pain and improve QoL.

Gepubliceerd: Int J Radiat Oncol Biol Phys 2015 Nov 1;93(3):694-701
Impact factor: 4.258

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12. No Increased Risk of Second Cancer After Radiotherapy in Patients Treated for Rectal or Endometrial Cancer in the Randomized TME, PORTEC-1, and PORTEC-2 Trials

Wiltink LM, Nout RA, Fiocco M, Meershoek-Klein Kranenbarg E, Jurgenliemk-Schulz IM, Jobsen JJ, Nagtegaal ID, Rutten HJ, van de Velde CJ, Creutzberg CL, Marijnen CA

Purpose: This study investigated the long-term probability of developing a second cancer in a large pooled cohort of patients treated with surgery with or without radiotherapy (RT).
Patients and Methods: All second cancers diagnosed in patients included in the TME, PORTEC-1, and PORTEC-2 trials were analyzed. In the TME trial, patients with rectal cancer (n = 1,530) were randomly allocated to preoperative external-beam RT (EBRT; 25 Gy in five fractions) or no RT. In the PORTEC trials, patients with endometrial cancer were randomly assigned to postoperative EBRT (46 Gy in 2-Gy fractions) versus no RT (PORTEC-1; n = 714) or EBRT versus vaginal brachytherapy (VBT; PORTEC-2; n = 427).
Results: A total of 2,554 patients were analyzed (median follow-up, 13.0 years; range 1.8 to 21.2 years). No differences were found in second cancer probability between patients who were treated without RT (10- and 15-year rates, 15.8% and 26.5%, respectively) and those treated with EBRT (10- and 15-year rates, 15.4% and 25.6%, respectively) or VBT (10-year rate, 14.9%). In the individual trials, no significant differences were found between treatment arms. All cancer survivors had a higher risk of developing a second cancer compared with an age- and sex-matched general population. The standardized incidence ratio for any second cancer was 2.98 (95% CI, 2.82 to 3.14).
Conclusion: In this pooled trial cohort of > 2,500 patients with pelvic cancers, those who underwent EBRT or VBT had no higher probability of developing a second cancer than patients who were treated with surgery alone. However, patients with rectal or endometrial cancer had an increased probability of developing a second cancer compared with the general population.

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Totale impact factor: 69.791
Gemiddelde impact factor: 5.816

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 15.742
Gemiddelde impact factor: 3.936

Reumatologie

1. Exploring preferences for domain-specific goal management in patients with polyarthritis: what to do when an important goal becomes threatened?
Arends RY, Bode C, Taal E, van de Laar MA

Usually priorities in goal management-intended to minimize discrepancies between a given and desired situation-are studied as person characteristics, neglecting possible domain-specific aspects. However, people may make different decisions in different situations depending on the importance of the personal issues at stake. Aim of the present study therefore was to develop arthritis-related vignettes to examine domain-specific goal management and to explore patients' preferences. Based on interviews and literature, situation-specific hypothetical stories were developed in which the main character encounters a problem with a valued goal due to arthritis. Thirty-one patients (61 % female, mean age 60 years) evaluated the face validity of the newly developed vignettes. Secondly, 262 patients (60 % female, mean age 63 years) were asked to come up with possible solutions for the problems with attaining a goal described in a subset of the vignettes. Goal management strategies within the responses and the preference for the various strategies were identified. The 11 developed vignettes in three domains were found to be face-valid. In 90 % of the responses, goal management strategies were identified (31 % goal maintenance, 29 % goal adjustment, 21 % goal disengagement, and 10 % goal re-engagement). Strategy preference was related to domains. Solutions containing goal disengagement were the least preferred. Using vignettes for measuring domain-specific goal management appears as valuable addition to the existing questionnaires. The vignettes can be used to study how patients with arthritis cope with threatened goals in specific domains from a patient's perspective. Domain-specific strategy preference emphasizes the importance of a situation-specific instrument.

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Impact factor: 1.516

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2. Foreword
Bardin T, van de Laar MA

Gepubliceerd: Joint Bone Spine 2015 Oct;82 Suppl 1:eS1
Impact factor: 2.901

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3. The Human and Economic Burden of Difficult-to-Treat Gouty Arthritis
Bardin T, Oude Voshaar MA, van de Laar MA

Gouty arthritis, one of the most painful and common forms of adult arthritis, is caused by monosodium urate crystal deposits in joints, most often in the lower extremities. Crystals trigger an inflammatory response leading to acute flares

characterized by a rapid onset of pain, warmth, swelling, and redness in involved joints. Over time, continued monosodium urate crystal deposits and inflammation can lead to chronic tophaceous gout that result in bone erosion, progressing to joint destruction and significant disability. The goal of therapy in an acute gout flare is prompt and safe termination of pain and inflammation. Acute gouty arthritis is usually treated with nonsteroidal anti-inflammatory drugs, colchicine, or corticosteroids. However, for a growing number of patients, current standard treatments are ineffective or are contraindicated, largely due to the presence of comorbidities. Gouty arthritis can have a major negative impact of health-related quality of life, especially in patients with difficult-to-treat disease, as revealed by recent studies comparing health-related quality of life with that of the general population. Additionally, gouty arthritis also constitutes an important economic burden through absence from work and medical costs. This burden is even greater in patients with difficult-to-treat disease.

Gepubliceerd: Joint Bone Spine 2015 Oct;82 Suppl 1:eS2-eS8
Impact factor: 2.901

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4. The Way Forward: Practical Clinical Considerations for the Use of Canakinumab in Patients With Difficult-to-Treat Gouty Arthritis
Bardin T, van de Laar MA

Canakinumab is indicated for patients with frequent gouty arthritis attacks who cannot be managed with standard-of-care medication, and should be used according to the labeled indication. Given its mechanism of action, physicians need to be aware of the potential contraindications and precautions with its use. When deciding as to whether a patient with gouty arthritis is an appropriate candidate for canakinumab treatment, several key clinical considerations should be kept in mind, which are discussed herein.

Gepubliceerd: Joint Bone Spine 2015 Oct;82 Suppl 1:eS30-eS32
Impact factor: 2.901

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5. Development of Multinational Definitions of Minimal Clinically Important Improvement and Patient Acceptable Symptomatic State in Osteoarthritis
Bellamy N, Hochberg M, Tubach F, Martin-Mola E, Awada H, Bombardier C, Hajjaj-Hassouni N, Logeart I, Matucci-Cerinic M, van de Laar M, van der Heijde D, Dougados M

Objective: The ability to interpret scores from patient-reported outcome measures at the individual patient level depends on the availability of valid, clinically meaningful benchmarks of response and state attainment. The goal was to develop multinational estimates for minimal clinically important improvement (MCII) and patient acceptable symptomatic state (PASS).
Methods: A multinational sample of patients with osteoarthritis (OA) was evaluated before and 4 weeks after treatment with nonsteroidal antiinflammatory drugs.

Patients completed either the Western Ontario and McMaster Osteoarthritis Index (WOMAC) numerical rating scale 3.1 (hip and knee OA) or the Australian/Canadian Index (AUSCAN) numerical rating scale 3.1 (hand OA) before and after treatment. Patients rated the clinical importance of their response to treatment and their satisfaction with the health state achieved, from which multinational MCII and PASS estimates were calculated for both the WOMAC and AUSCAN indices.
Results: A total of 609 patients from 7 countries participated in the study. MCII and PASS estimates varied slightly by instrument and subscale. Absolute (percentage) change for MCII ranged 6-9 (10% to 17%) for WOMAC and 4-9 (8% to 15%) for AUSCAN. PASS estimates ranged 39-48 for WOMAC and 38-45 for AUSCAN. Some between-country variation was observed in MCII and PASS.
Conclusion: Preliminary multinational estimates for MCII and PASS have been developed for several countries. Further research is required to evaluate the robustness, temporal consistency, and age- and sex-dependency of the preliminary estimates as well as their generalizability to other countries, languages, cultures, regions, and other condition-specific outcome measures.

Gepubliceerd: Arthritis Care Res (Hoboken) 2015 Jul;67(7):972-80
Impact factor: 4.713

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6. Inadequate pain relief and large functional loss among patients with knee osteoarthritis: evidence from a prospective multinational longitudinal study of osteoarthritis real-world therapies
Conaghan PG, Peloso PM, Everett SV, Rajagopalan S, Black CM, Mavros P, Arden NK, Phillips CJ, Rannou F, van de Laar MA, Moore RA, Taylor SD

Objective: To estimate the prevalence of inadequate pain relief (IPR) among patients with symptomatic knee OA prescribed analgesic therapy and to characterize patients with IPR.
Methods: Patients >/=50 years old with physician-diagnosed knee OA who had taken topical or oral pain medication for at least 14 days were recruited for this prospective non-interventional study in six European countries. Pain and function were assessed using the Brief Pain Inventory (BPI) and the WOMAC; quality of life (QoL) was assessed using the 12-item short form. IPR was defined as an average pain score of >4 out of 10 on BPI question 5.
Results: Of 1187 patients enrolled, 68% were female and the mean age was 68 years (s.d. 9); 639 (54%) met the definition of IPR. Patient responses for the BPI average pain question were well correlated with responses on the WOMAC pain subscale (Spearman r = 0.64, P < 0.001). In multivariate logistic regression, patients with IPR had greater odds of being female [adjusted odds ratio (adjOR) 1.90 (95% CI 1.46, 2.48)] and having OA in both knees [adjOR 1.48 (95% CI 1.15, 1.90)], higher BMI, longer OA duration, depression or diabetes. Patients with IPR (vs non-IPR) were more likely to have worse QoL, greater function loss and greater pain interference.
Conclusion: IPR is common among patients with knee OA requiring analgesics and is associated with large functional loss and impaired QoL. Patients at particular risk of IPR, as characterized in this study, may require greater attention towards their

analgesic treatment options. Trial registration: https://clinicaltrials.gov/ (NCT01294696).

Gepubliceerd: Rheumatology (Oxford) 2015;54(2):270-7
Impact factor: 4.475

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7. Measuring the Therapeutic Relationship in Internet-Based Interventions
Ferwerda M, van Beugen S, van Riel PC, van de Kerkhof PC, de Jong EM, Smit JV, Zeeuwen-Franssen ME, Kroft EB, Visser H, Vonkeman HE, Creemers MC, van Middendorp H, Evers AW

Gepubliceerd: Psychother Psychosom 2015 Nov 27;85(1):47-9
Impact factor: 9.196

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8. The EULAR Study Group for Registers and Observational Drug Studies: comparability of the patient case mix in the European biologic disease modifying anti-rheumatic drug registers
Kearsley-Fleet L, Zavada J, Hetland ML, Nordstrom DC, Aaltonen KJ, Listing J, Zink A, Gati T, Rojkovich B, Iannone F, Gremese E, van Riel PL, van de Laar MA, Lie E, Kvien TK, Canhao H, Fonseca JE, Rotar Z, Loza E, Carmona L, Askling J, Johansson K, Finckh A, Dixon WG, Hyrich KL

Objective: Under the auspices of the European League Against Rheumatism (EULAR), a study group of investigators representing European biologic DMARD (bDMARD) registers was convened. The purpose of this initial assessment was to collect and compare a cross section of patient characteristics and collate information on the availability of potential confounders within these registers.
Methods: Baseline characteristics of patients starting their first bDMARD in an arbitrary year (2008) for the treatment of RA, including demographic and disease characteristics, bDMARD drug details and co-morbidities, were collected and compared across 14 European bDMARD registers.
Results: A total of 5320 patients were included. Half the registers had restricted recruitment to certain bDMARDs during the study year. All registers` collected data on age, gender, disease duration, seropositivity for IgM-RF and 28-joint DAS (DAS28). The mean DAS28 ranged from 4.2 to 6.6 and the mean HAQ from 0.8 to 1.9. Current smoking ranged from 9% to 34%. Nine registers reported co-morbidities with varying prevalence.
Conclusion: In addition to demonstrating European-wide collaboration across rheumatology bDMARD registers, this assessment identified differences in prescribing patterns, recruitment strategies and data items collected. These differences need to be considered when applying strategies for combined analysis. The lack of a common data model across Europe calls for further work to harmonize data collection across registers.

Gepubliceerd: Rheumatology (Oxford) 2015;54(6):1074-9
Impact factor: 4.475

9. Neuropathic-like pain features and cross-sectional associations in rheumatoid arthritis
Koop SM, Ten Klooster PM, Vonkeman HE, Steunebrink LM, van de Laar MA

Introduction: Increasing evidence indicates that features suggestive of neuropathic pain may also be present in patients with common rheumatic conditions. The objective of this study was to examine neuropathic-like pain symptoms and associated factors in patients with rheumatoid arthritis.
Methods: We used the painDETECT screening tool to identify possible or likely neuropathic pain in 159 outpatients with rheumatoid arthritis. Patients additionally completed other self-reported measures, while clinical measures were assessed to calculate the 28-joint Disease Activity Score. Univariate analyses and multivariable logistic regression were used to identify factors associated with neuropathic pain features.
Results: According to the painDETECT, 27 patients (17.0 %) were classified as having likely neuropathic pain and 34 patients (21.4 %) as having possible neuropathic pain. Besides reporting more severe pain, patients with likely or possible neuropathic pain were more likely to meet the diagnostic criteria for fibromyalgia, to use analgesics, and to have more tender joints and a worse physical and mental health status as measured by the 36-item Short-Form health survey. In multivariable analysis, physical ($P < 0.001$) and mental health status ($P = 0.006$) remained significantly associated with neuropathic pain features, even after controlling for pain severity.
Conclusions: These findings suggest that a sizeable proportion of patients with relatively well-controlled rheumatoid arthritis report symptoms suggestive of neuropathic pain. Neuropathic-like pain symptoms are independently associated with worse self-reported physical and mental health.

Gepubliceerd: Arthritis Res Ther 2015;17:237
Impact factor: 3.753

10. Cost-effectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial
Manders SH, Kievit W, Adang E, Brus HL, Moens HJ, Hartkamp A, Hendriks L, Brouwer E, Visser H, Vonkeman HE, Hendrikx J, Jansen TL, Westhovens R, van de Laar MA, van Riel PL

I**ntroduction:** For patients with rheumatoid arthritis (RA) whose treatment with a tumour necrosis factor inhibitor (TNFi) is failing, several biological treatment options are available. Often, another TNFi or a biological with another mode of action is prescribed. The objective of this study was to compare the effectiveness and cost-effectiveness of three biologic treatments with different modes of action in patients with RA whose TNFi therapy is failing.

Methods: We conducted a pragmatic, 1-year randomised trial in a multicentre setting. Patients with active RA despite previous TNFi treatment were randomised to receive abatacept, rituximab or a different TNFi. The primary outcome (Disease Activity Score in 28 joints) and the secondary outcomes (Health Assessment Questionnaire Disability Index and 36-item Short Form Health Survey scores) were analysed using linear mixed models. Cost-effectiveness was analysed on the basis of incremental net monetary benefit, which was based on quality-adjusted life-years (calculated using EQ-5D scores), and all medication expenditures consumed in 1 year. All analyses were also corrected for possible confounders.
Results: Of 144 randomised patients, 5 were excluded and 139 started taking abatacept (43 patients), rituximab (46 patients) or a different TNFi (50 patients). There were no significant differences between the three groups with respect to multiple measures of RA outcomes. However, our analysis revealed that rituximab therapy is significantly more cost-effective than both abatacept and TNFi over a willingness-to-pay range of 0 to 80,000 euros.
Conclusions: All three treatment options were similarly effective; however, when costs were factored into the treatment decision, rituximab was the best option available to patients whose first TNFi treatment failed. However, generalization of these costs to other countries should be undertaken carefully.
Trial registration: Netherlands Trial Register number NTR1605. Registered 24 December 2008.

Gepubliceerd: Arthritis Res Ther 2015;17:134
Impact factor: 3.753

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11. Effectiveness of TNF inhibitor treatment with various methotrexate doses in patients with rheumatoid arthritis: results from clinical practice
Manders SH, Kievit W, Adang E, Jansen TJ, Stolk JN, Visser H, Schilder AM, Vonkeman HE, van de Laar MA, van Riel PL

Gepubliceerd: Ann Rheum Dis 2015;74(3):e24
Impact factor: 10.377

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12. Tapering and discontinuation of methotrexate in patients with RA treated with TNF inhibitors: data from the DREAM registry
Manders SH, van de Laar MA, Rongen-van Dartel SA, Bos R, Visser H, Brus HL, Jansen T, Vonkeman HE, van Riel PL, Kievit W

Objectives: To study the number of patients that taper or discontinue concomitant methotrexate (MTX) in daily practice in patients with rheumatoid arthritis (RA) treated with tumour necrosis factor inhibitor (TNFi) and to analyse the effects of that adaption on disease activity and drug survival.
Methods: Data were collected from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. Patients who started their first TNFi were included in the study. Treatment effectiveness after MTX tapering or discontinuation was analysed using

Disease Activity Score of 28 joints (DAS28). Drug survival of the TNFi was analysed using the Cox proportional hazard model with a time-dependent covariate.
Results: In 458 patients (34%), MTX was tapered, 126 patients (10%) discontinued MTX and 747 patients (56%) continued MTX at the same dose. On average, DAS28 improved after tapering MTX (-0.40, -0.45) and after stopping MTX (-0.28, -0.12) at 6 and 12 months. In the taper group, 21% of the patients relapsed (DAS28 increase >0.6), and in the discontinuation group this was 21% and 24% at 6 and 12 months, respectively. Patients who taper and discontinue MTX have a similar DAS28 score over time as patients who continue MTX. Moreover, there was no influence of tapering or discontinuation of MTX on long-term drug survival of TNFi.
Conclusions: In daily practice, tapering or discontinuation of concomitant MTX in patients with RA treated with TNFi frequently occurs and it does not seem to influence the average DAS28 over time or the long-term TNFi drug survival. It appears that in daily clinical practice the correct patients are selected to taper or discontinue MTX.

Gepubliceerd: RMD Open 2015;1(1):e000147
Impact factor: 0

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13. Construct Validation of a Multidimensional Computerized Adaptive Test for Fatigue in Rheumatoid Arthritis
Nikolaus S, Bode C, Taal E, Vonkeman HE, Glas CA, van de Laar MA

Objective: Multidimensional computerized adaptive testing enables precise measurements of patient-reported outcomes at an individual level across different dimensions. This study examined the construct validity of a multidimensional computerized adaptive test (CAT) for fatigue in rheumatoid arthritis (RA).
Methods: The 'CAT Fatigue RA' was constructed based on a previously calibrated item bank. It contains 196 items and three dimensions: 'severity', 'impact' and 'variability' of fatigue. The CAT was administered to 166 patients with RA. They also completed a traditional, multidimensional fatigue questionnaire (BRAF-MDQ) and the SF-36 in order to examine the CAT's construct validity. A priori criterion for construct validity was that 75% of the correlations between the CAT dimensions and the subscales of the other questionnaires were as expected. Furthermore, comprehensive use of the item bank, measurement precision and score distribution were investigated.
Results: The a priori criterion for construct validity was supported for two of the three CAT dimensions (severity and impact but not for variability). For severity and impact, 87% of the correlations with the subscales of the well-established questionnaires were as expected but for variability, 53% of the hypothesised relations were found. Eighty-nine percent of the items were selected between one and 137 times for CAT administrations. Measurement precision was excellent for the severity and impact dimensions, with more than 90% of the CAT administrations reaching a standard error below 0.32. The variability dimension showed good measurement precision with 90% of the CAT administrations reaching a standard error below 0.44. No floor- or ceiling-effects were found for the three dimensions.

Conclusion: The CAT Fatigue RA showed good construct validity and excellent measurement precision on the dimensions severity and impact. The dimension variability had less ideal measurement characteristics, pointing to the need to recalibrate the CAT item bank with a two-dimensional model, solely consisting of severity and impact.

Gepubliceerd: PLoS One 2015;10(12):e0145008
Impact factor: 3.234

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14. Working mechanism of a multidimensional computerized adaptive test for fatigue in rheumatoid arthritis
Nikolaus S, Bode C, Taal E, Vonkeman HE, Glas CA, van de Laar MA

Background: This paper demonstrates the mechanism of a multidimensional computerized adaptive test (CAT) to measure fatigue in patients with rheumatoid arthritis (RA). A CAT can be used to precisely measure patient-reported outcomes at an individual level as items are consequentially selected based on the patient's previous answers. The item bank of the CAT Fatigue RA has been developed from the patients' perspective and consists of 196 items pertaining to three fatigue dimensions: severity, impact and variability of fatigue.
Methods: The CAT Fatigue RA was completed by fifteen patients. To test the CAT's working mechanism, we applied the flowchart-check-method. The adaptive item selection procedure for each patient was checked by the researchers. The estimated fatigue levels and the measurement precision per dimension were illustrated with the selected items, answers and flowcharts.
Results: The CAT Fatigue RA selected all items in a logical sequence and those items were selected which provided the most information about the patient's individual fatigue. Flowcharts further illustrated that the CAT reached a satisfactory measurement precision, with less than 20 items, on the dimensions severity and impact and to somewhat lesser extent also for the dimension variability. Patients' fatigue scores varied across the three dimensions; sometimes severity scored highest, other times impact or variability. The CAT's ability to display different fatigue experiences can improve communication in daily clinical practice, guide interventions, and facilitate research into possible predictors of fatigue.
Conclusions: The results indicate that the CAT Fatigue RA measures precise and comprehensive. Once it is examined in more detail in a consecutive, elaborate validation study, the CAT will be available for implementation in daily clinical practice and for research purposes.

Gepubliceerd: Health Qual Life Outcomes 2015;13:23
Impact factor: 2.120

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15. Patients' considerations in the decision-making process of initiating disease-modifying anti-rheumatic drugs
Nota I, Drossaert CH, Taal E, van de Laar MA

Objectives: To explore what considerations patients have when deciding about disease-modifying anti-rheumatic drugs (DMARDs) and what information patients need to participate in the decision-making process.
Methods: In-depth face-to-face interviews were conducted with 32 inflammatory arthritis patients who recently consulted their rheumatologist and discussed initiating DMARDs.
Results: Beliefs in the necessity of DMARDs, either for relief of symptoms or prevention of future joint damage, were reasons to initiate DMARDs. Furthermore, trust in the rheumatologist and the healthcare system was important in this respect. Patients expressed many concerns about initiating DMARDS. These related to the perceived aggressive and harmful nature of DMARDs, potential (or unknown) side effects, influence on fertility and pregnancy, combination with other medicines, time to benefit and manner of administration. Participants also worried about the future: about long term medication use and the feeling of dependency, and, -if this medicine proved to be ineffective-, about the risks of future treatments and running out of options. To decrease this uncertainty, participants wanted to be informed about multiple treatment options, both current and future. They did not only want clinical information, but also information on how the medications could affect their daily lives.
Conclusion: Health education should inform patients about multiple treatment options, for the current time being as well as for the future. It should enable patients to compare treatments with regards to both clinical aspects as well as possible consequences for their daily lives.

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Impact factor: 4.713

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16. Assessment of fatigue in rheumatoid arthritis: a psychometric comparison of single-item, multiitem, and multidimensional measures
Oude Voshaar MA, Ten Klooster PM, Bode C, Vonkeman HE, Glas CA, Jansen T, van Albada-Kuipers I, van Riel PL, van de Laar MA

Objective: To compare the psychometric functioning of multidimensional disease-specific, multiitem generic, and single-item measures of fatigue in patients with rheumatoid arthritis (RA).
Methods: Confirmatory factor analysis (CFA) and longitudinal item response theory (IRT) modeling were used to evaluate the measurement structure and local reliability of the Bristol RA Fatigue Multi-Dimensional Questionnaire (BRAF-MDQ), the Medical Outcomes Study Short Form-36 (SF-36) vitality scale, and the BRAF Numerical Rating Scales (BRAF-NRS) in a sample of 588 patients with RA.
Results: A 1-factor CFA model yielded a similar fit to a 5-factor model with subscale-specific dimensions, and the items from the different instruments adequately fit the IRT model, suggesting essential unidimensionality in measurement. The SF-36 vitality scale outperformed the BRAF-MDQ at lower levels of fatigue, but was less precise at moderate to higher levels of fatigue. At these levels of fatigue, the living, cognition, and emotion subscales of the BRAF-MDQ

provide additional precision. The BRAF-NRS showed a limited measurement range with its highest precision centered on average levels of fatigue.
Conclusion: The different instruments appear to access a common underlying domain of fatigue severity, but differ considerably in their measurement precision along the continuum. The SF-36 vitality scale can be used to measure fatigue severity in samples with relatively mild fatigue. For samples expected to have higher levels of fatigue, the multidimensional BRAF-MDQ appears to be a better choice. The BRAF-NRS are not recommended if precise assessment is required, for instance in longitudinal settings.

Gepubliceerd: J Rheumatol 2015 Mar;42(3):413-20
Impact factor: 3.187

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17. Validity and measurement precision of the PROMIS physical function item bank and a content validity-driven 20-item short form in rheumatoid arthritis compared with traditional measures
Oude Voshaar MA, Ten Klooster PM, Glas CA, Vonkeman HE, Taal E, Krishnan E, Bernelot Moens HJ, Boers M, Terwee CB, van Riel PL, van de Laar MA

Objective: To evaluate the content validity and measurement properties of the Patient-Reported Outcome Measurement Information System (PROMIS) physical function item bank and a 20-item short form in patients with RA in comparison with the HAQ disability index (HAQ-DI) and 36-item Short Form Health Survey (SF-36) physical functioning scale (PF-10).
Methods: The content validity of the instruments was evaluated by linking their items to the International Classification of Functioning, Disability and Health (ICF) core set for RA. The measures were administered to 690 RA patients enrolled in the Dutch Rheumatoid Arthritis Monitoring registry. Measurement precision was evaluated using item response theory methods and construct validity was evaluated by correlating physical function scores with other clinical and patient-reported outcome measures.
Results: All 207 health concepts identified in the physical function measures referred to activities that are featured in the ICF. Twenty-three of 26 ICF RA core set domains are featured in the full PROMIS physical function item bank compared with 13 and 8 for the HAQ-DI and PF-10, respectively. As hypothesized, all three physical function instruments were highly intercorrelated (r 0.74-0.84), moderately correlated with disease activity measures (r 0.44-0.63) and weakly correlated with age (rs 0.07-0.14). Item response theory-based analysis revealed that a 20-item PROMIS physical function short form covered a wider range of physical function levels than the HAQ-DI or PF-10.
Conclusion: The PROMIS physical function item bank demonstrated excellent measurement properties in RA. A content-driven 20-item short form may be a useful tool for assessing physical function in RA.

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Impact factor: 4.475

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18. Comparison of 2 Dosages of Intraarticular Triamcinolone for the Treatment of Knee Arthritis: Results of a 12-week Randomized Controlled Clinical Trial
Popma JW, Snel FW, Haagsma CJ, Brummelhuis-Visser P, Oldenhof HG, van der Palen J, van de Laar MA

Objective: To determine whether a double dose of intraarticular triamcinolone acetonide is more effective for knee arthritis than a 40-mg dose.
Methods: In this 12-week randomized controlled clinical trial, 40 mg and 80 mg of intraarticular triamcinolone acetonide were compared in patients with knee arthritis. Evaluated variables included a Likert burden scale, visual analog scale pain scale, degree of arthritis activity, presence of swelling, and presence of functional limitation.
Results: Ninety-seven patients were randomized. No significant differences were observed between the groups regarding any outcomes.
Conclusion: An 80-mg dose of triamcinolone acetonide had no additional benefit compared with 40 mg as treatment for knee arthritis.
Trial registration: Nederlands Trial Register; trial registration number: NTR2298.

Gepubliceerd: J Rheumatol 2015 Aug 1;42(10):1865-8
Impact factor: 3.187

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19. Predictors of satisfactory improvements in pain for patients with early rheumatoid arthritis in a treat-to-target study
Ten Klooster PM, Vonkeman HE, Oude Voshaar MA, Siemons L, van Riel PL, van de Laar MA

Objective: The aim of this study was to identify baseline predictors of achieving patient-perceived satisfactory improvement (PPSI) in pain after 6 months of treat to target in patients with early RA.
Methods: Baseline and 6 month data were used from patients included in the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. Simple and multivariable logistic regression analyses were used to identify significant predictors of achieving an absolute improvement of 30 mm or a relative improvement of 50% on a visual analogue scale for pain.
Results: At 6 months, 125 of 209 patients (59.8%) achieved an absolute PPSI and 130 patients (62.2%) achieved a relative PPSI in pain. Controlling for baseline pain, having symmetrical arthritis was the strongest independent predictor of achieving an absolute [odds ratio (OR) 3.17, P = 0.03] or relative (OR 3.44, P = 0.01) PPSI. Additionally, anti-CCP positivity (OR 2.04, P = 0.04) and having </=12 tender joints (OR 0.29, P = 0.01) were predictive of achieving a relative PPSI. The total explained variance of baseline predictors was 30% for absolute and 18% for relative improvements, respectively.
Conclusion: Symmetrical joint involvement, anti-CCP positivity and fewer tender joints at baseline are prognostic signs for achieving satisfactory improvement in pain after 6 months of treat to target in patients with early RA.

Gepubliceerd: Rheumatology (Oxford) 2015;54(6):1080-6
Impact factor: 4.475

20. Impact on total population health and societal cost, and the implication on the actual cost-effectiveness of including tumour necrosis factor-alpha antagonists in management of ankylosing spondylitis: a dynamic population modelling study

Tran-Duy A, Boonen A, van de Laar MA, Severens JL

Background: Sequential treatment of ankylosing spondylitis (AS) that includes tumour necrosis factor-alpha antagonists (anti-TNF agents) has been applied in most of the Western countries. Existing cost-effectiveness (CE) models almost exclusively presented the incremental CE of anti-TNF agents using a closed cohort while budget impact studies are mainly lacking. Notwithstanding, information on impact on total population health and societal budget as well as on actual incremental CE for a given decision time span are important for decision makers. This study aimed at quantifying, for different decision time spans starting from January 1, 2014 in the Dutch society, (1) impact of sequential drug treatment strategies without and with inclusion of anti-TNF agents (Strategies 1 and 2, respectively) on total population health and societal cost, and (2) the actual incremental CE of Strategy 2 compared to Strategy 1.
Methods: Dynamic population modelling was used to capture total population health and cost, and the actual incremental CE. Distinguishing the prevalent AS population on January 1, 2014 and the incident AS cohorts in the subsequent 20 years, the model tracked individually an actual number of AS patients until death or end of the simulation time. During the simulation, data on patient characteristics, history of drug use, costs and health at discrete time points were generated. In Strategy 1, five nonsteroidal anti-inflammatory drugs (NSAIDs) were available but anti-TNF agents withdrawn. In Strategy 2, five NSAIDs and two anti-TNF agents continued to be available.
Results: The predicted size of the prevalent AS population in the Dutch society varied within the range of 67,145-69,957 with 44-46 % of the patients receiving anti-TNF agents over the period 2014-2034. The use of anti-TNF agents resulted in an increase in the annual drug costs (168.54-205.28 million Euros), but at the same time caused a decrease in the annual productivity costs (12.58-31.21 million Euros) and in annual costs of healthcare categories other than drugs (7.23-11.90 million Euros). Incremental cost (Euros) per QALY gained in Strategy 2 compared to Strategy 1 corresponding to decision time spans of 5, 10, 15 and 20 years improved slightly from 75,379 to 67,268, 63,938 and 61,129, respectively. At willingness-to-pay thresholds of 118,656, 112,067, 110,188 and 110,512 Euros, it was 99 % certain that Strategy 2 was cost-effective for decision time spans of 5, 10, 15 and 20, respectively.
Conclusions: Using the dynamic population approach, the present model can project real-time data to inform a healthcare system decision that affects all actual number of AS patients eligible for anti-TNF agents within different decision time spans. The predicted total population costs of different categories in the present

study can help plan the organization of the healthcare resources based on the national budget for the disease.

Gepubliceerd: Cost Eff Resour Alloc 2015;13:18
Impact factor: 0

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21. Estimation of heritability of different outcomes for genetic studies of TNFi response in patients with rheumatoid arthritis
Umicevic Mirkov M, Janss L, Vermeulen SH, van de Laar MA, van Riel PL, Guchelaar HJ, Brunner HG, Albers CA, Coenen MJ

Objectives: Pharmacogenetic studies of tumour necrosis factor inhibitors (TNFi) response in patients with rheumatoid arthritis (RA) have largely relied on the changes in complex disease scores, such as disease activity score 28 (DAS28), as a measure of treatment response. It is expected that genetic architecture of such complex score is heterogeneous and not very suitable for pharmacogenetic studies. We aimed to select the most optimal phenotype for TNFi response using heritability estimates.
Methods: Using two linear mixed-modelling approaches (Bayz and GCTA), we estimated heritability, together with genomic and environmental correlations for the TNFi drug-response phenotype DeltaDAS28 and its separate components: Delta swollen joint count (SJC), Delta tender joint count (TJC), Delta erythrocyte sedimentation rate (ESR) and Delta visual-analogue scale of general health (VAS-GH). For this, we used genome-wide single nucleotide polymorphism (SNP) data from 878 TNFi-treated Dutch patients with RA. Furthermore, a multivariate genome-wide association study (GWAS) approach was implemented, analysing separate DAS28 components simultaneously.
Results: The highest heritability estimates were found for DeltaSJC ([Formula: see text]=0.76 and [Formula: see text]=0.87) and DeltaTJC ([Formula: see text]=0.62 and [Formula: see text]=0.82); lower heritability was found for DeltaDAS28 ([Formula: see text]=0.59 and [Formula: see text]=0.71) while estimates for DeltaESR and DeltaVASGH were near or equal to zero. The highest genomic correlations were observed for DeltaSJC and DeltaTJC (0.49), and the highest environmental correlation was seen between DeltaTJC and DeltaVASGH (0.62). The multivariate GWAS did not generate excess of low p values as compared with a univariate analysis of DeltaDAS28.
Conclusions: Our results indicate that multiple SNPs together explain a substantial portion of the variation in change in joint counts in TNFi-treated patients with RA. In conclusion, of the outcomes studied, the joint counts are most suitable for TNFi pharmacogenetics in RA.

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Impact factor: 10.377

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22. Associations of markers of matrix metabolism, inflammation markers, and adipokines with superior cam deformity of the hip and their relation with future hip osteoarthritis
van Spil WE, Agricola R, Drossaers-Bakker KW, Weinans H, Lafeber FP

Objective: First, to study how markers of matrix metabolism, inflammation markers, and adipokines relate to (superior) cam deformity and (possible) cam impingement of the hip. Second, to investigate whether they can identify subjects with cam deformity that are at risk of future hip osteoarthritis (OA). METHOD: In a cohort of 1002 subjects (CHECK), (superior) cam deformity was defined by an alpha angle >60 degrees on anteroposterior pelvic radiographs and (possible) cam impingement by a cam deformity together with internal hip rotation </=20 degrees . Hip OA at 5-year follow-up was defined by Kellgren and Lawrence grade >/=2 or total hip replacement.
Results: Subjects with (superior) cam deformity and (possible) cam impingement showed lower levels of bone turnover markers (uCTX-I, uNTX-I, sPINP, sOC) than those without. Cam deformity was positively associated with future hip OA, but associations were weaker at high levels of bone turnover. sCOMP and sHA levels were higher in subjects with cam deformity, while other cartilage and synovium markers were not. Some markers of inflammation (pLeptin, pAdiponectin, and erythrocyte sedimentation rate) were lower in presence of cam deformity and cam impingement, but high-sensitivity C-reactive protein was not. Most associations depended largely on gender differences.
Conclusion: Bone metabolism may be relevant in the pathogenesis of (superior) cam deformity and in the development of (superior) cam deformity into hip OA. Subjects with cam deformity and cam impingement surprisingly showed lower levels of inflammation markers and adipokines. Associations of cartilage turnover markers with cam deformity and cam impingement were less obvious.

Gepubliceerd: Osteoarthritis Cartilage 2015 Nov;23(11):1897-905
Impact factor: 4.165

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23. Patient-centred care in established rheumatoid arthritis
Oude Voshaar M, Nota I, van de Laar MA, van den Bemt BJ

Review of the evidence on patient-centred care (PCC) in rheumatoid arthritis (RA) shows that involving the patient as an individual - with unique needs, concerns and preferences - has a relevant impact on treatment outcomes (safety, effectiveness and costs). This approach empowers patients to take personal responsibility for their treatment. Because clinicians are only able to interact personally with their patients just a few hours per year, patients with a chronic condition such as RA should be actively involved in the management of their disease. To stimulate this active role, five different PCC activities can be distinguished: (1) patient education, (2) patient involvement/shared decision-making, (3) patient empowerment/self-management, (4) involvement of family and friends and (5) physical and emotional support. This article reviews the existing knowledge on these five PCC activities in the context of

established RA management, especially focused on opportunities to increase medication adherence in established RA.

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Impact factor: 2.603

Totale impact factor: 93.497
Gemiddelde impact factor: 4.065

Aantal artikelen 1e, 2e of laatste auteur:
Totale impact factor: 45.987
Gemiddelde impact factor:

Revalidatiegeneeskunde

1. Effect of power-assisted hand-rim wheelchair propulsion on shoulder load in experienced wheelchair users: A pilot study with an instrumented wheelchair
Kloosterman MG, Buurke JH, de Vries W, Van der Woude LH, Rietman JS

This study aims to compare hand-rim and power-assisted hand-rim propulsion on potential risk factors for shoulder overuse injuries: intensity and repetition of shoulder loading and force generation in the extremes of shoulder motion. Eleven experienced hand-rim wheelchair users propelled an instrumented wheelchair on a treadmill while upper-extremity kinematic, kinetic and surface electromyographical data was collected during propulsion with and without power-assist. As a result during power-assisted propulsion the peak resultant force exerted at the hand-rim decreased and was performed with significantly less abduction and internal rotation at the shoulder. At shoulder level the anterior directed force and internal rotation and flexion moments decreased significantly. In addition, posterior and the minimal inferior directed forces and the external rotation moment significantly increased. The stroke angle decreased significantly, as did maximum shoulder flexion, extension, abduction and internal rotation. Stroke-frequency significantly increased. Muscle activation in the anterior deltoid and pectoralis major also decreased significantly. In conclusion, compared to hand-rim propulsion power-assisted propulsion seems effective in reducing potential risk factors of overuse injuries with the highest gain on decreased range of motion of the shoulder joint, lower peak propulsion force on the rim and reduced muscle activity.

Gepubliceerd: Med Eng Phys 2015 Aug 22;37(10):961-6
Impact factor: 1.825

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2. Feasibility study into self-administered training at home using an arm and hand device with motivational gaming environment in chronic stroke
Nijenhuis SM, Prange GB, Amirabdollahian F, Sale P, Infarinato F, Nasr N, Mountain G, Hermens HJ, Stienen AH, Buurke JH, Rietman JS

Background: Assistive and robotic training devices are increasingly used for rehabilitation of the hemiparetic arm after stroke, although applications for the wrist and hand are trailing behind. Furthermore, applying a training device in domestic settings may enable an increased training dose of functional arm and hand training. The objective of this study was to assess the feasibility and potential clinical changes associated with a technology-supported arm and hand training system at home for patients with chronic stroke.
Methods: A dynamic wrist and hand orthosis was combined with a remotely monitored user interface with motivational gaming environment for self-administered training at home. Twenty-four chronic stroke patients with impaired arm/hand function were recruited to use the training system at home for six weeks. Evaluation of feasibility involved training duration, usability and motivation. Clinical outcomes on

arm/hand function, activity and participation were assessed before and after six weeks of training and at two-month follow-up.
Results: Mean System Usability Scale score was 69 % (SD 17 %), mean Intrinsic Motivation Inventory score was 5.2 (SD 0.9) points, and mean training duration per week was 105 (SD 66) minutes. Median Fugl-Meyer score improved from 37 (IQR 30) pre-training to 41 (IQR 32) post-training and was sustained at two-month follow-up (40 (IQR 32)). The Stroke Impact Scale improved from 56.3 (SD 13.2) pre-training to 60.0 (SD 13.9) post-training, with a trend at follow-up (59.8 (SD 15.2)). No significant improvements were found on the Action Research Arm Test and Motor Activity Log.
Conclusions: Remotely monitored post-stroke training at home applying gaming exercises while physically supporting the wrist and hand showed to be feasible: participants were able and motivated to use the training system independently at home. Usability shows potential, although several usability issues need further attention. Upper extremity function and quality of life improved after training, although dexterity did not. These findings indicate that home-based arm and hand training with physical support from a dynamic orthosis is a feasible tool to enable self-administered practice at home. Such an approach enables practice without dependence on therapist availability, allowing an increase in training dose with respect to treatment in supervised settings.
Trial registration: This study has been registered at the Netherlands Trial Registry (NTR): NTR3669.

Gepubliceerd: J Neuroeng Rehabil 2015;12:89
Impact factor: 2.740

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3. Rolling resistance and propulsion efficiency of manual and power-assisted wheelchairs
Pavlidou E, Kloosterman MG, Buurke JH, Rietman JS, Janssen TW

Rolling resistance is one of the main forces resisting wheelchair propulsion and thus affecting stress exerted on the upper limbs. The present study investigates the differences in rolling resistance, propulsion efficiency and energy expenditure required by the user during power-assisted and manual propulsion. Different tire pressures (50%, 75%, 100%) and two different levels of motor assistance were tested. Drag force, energy expenditure and propulsion efficiency were measured in 10 able-bodied individuals under different experimental settings on a treadmill. Results showed that drag force levels were significantly higher in the 50%, compared to the 75% and 100% inflation conditions. In terms of wheelchair type, the manual wheelchair displayed significantly lower drag force values than the power-assisted one. The use of extra-power-assisted wheelchair appeared to be significantly superior to conventional power-assisted and manual wheelchairs concerning both propulsion efficiency and energy expenditure required by the user. Overall, the results of the study suggest that the use of power-assisted wheelchair was more efficient and required less energy input by the user, depending on the motor assistance provided.

Gepubliceerd: Med Eng Phys 2015 Sep 12;37(11):1105-10
Impact factor: 1.825

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4. The Effect of Arm Support Combined With Rehabilitation Games on Upper-Extremity Function in Subacute Stroke: A Randomized Controlled Trial
Prange GB, Kottink AI, Buurke JH, Eckhardt MM, van Keulen-Rouweler BJ, Ribbers GM, Rietman JS

Background: Use of rehabilitation technology, such as (electro)mechanical devices or robotics, could partly relieve the increasing strain on stroke rehabilitation caused by an increasing prevalence of stroke. Arm support (AS) training showed improvement of unsupported arm function in chronic stroke.
Objective: To examine the effect of weight-supported arm training combined with computerized exercises on arm function and capacity, compared with dose-matched conventional reach training in subacute stroke patients.
Methods: In a single-blind, multicenter, randomized controlled trial, 70 subacute stroke patients received 6 weeks of training with either an AS device combined with computerized exercises or dose-matched conventional training (CON). Arm function was evaluated pretraining and posttraining by Fugl-Meyer assessment (FM), maximal reach distance, Stroke Upper Limb Capacity Scale (SULCS), and arm pain via Visual Analogue Scale, in addition to perceived motivation by Intrinsic Motivation Inventory posttraining.
Results: FM and SULCS scores and reach distance improved significantly within both groups. These improvements and experienced pain did not differ between groups. The AS group reported higher interest/enjoyment during training than the CON group.
Conclusions: AS training with computerized exercises is as effective as conventional therapy dedicated to the arm to improve arm function and activity in subacute stroke rehabilitation, when applied at the same dose.

Gepubliceerd: Neurorehabil Neural Repair 2015;29(2):174-82
Impact factor: 3.976

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5. Influence of a user-adaptive prosthetic knee on quality of life, balance confidence, and measures of mobility: a randomised cross-over trial
Prinsen EC, Nederhand MJ, Olsman J, Rietman JS

Objective: To study the influence of a transition from a non-microprocessor controlled to the Rheo Knee(R) II on quality of life, balance confidence and measures of mobility.
Design: Randomised crossover trial.
Setting: Research department of a rehabilitation centre.
Subjects: Persons with a transfemoral amputation or knee disarticulation (n=10).
Interventions: Participants were assessed with their own non-microprocessor controlled knee and with the Rheo Knee(R) II. The low-profile Vari-Flex with EVO

foot was installed in both knee conditions, followed by eight weeks of acclimatisation. The order in which knees were tested was randomised.
Main measures: Prosthesis Evaluation Questionnaire with addendum, Activities-specific Balance Confidence scale, Timed "up & go" test, Timed up and down stairs test, Hill Assessment Index, Stairs Assessment Index, Standardized Walking Obstacle Course and One Leg Balance test.
Results: Significant higher scores were found for the Rheo Knee(R) II on the Residual Limb Health subscale of the Prosthesis Evaluation Questionnaire when compared to the non-microprocessor controlled prosthetic knee (median [interquartile range] resp. 86.67 [62.21-93.08] and 68.71 [46.15-94.83]; P=0.047) In addition, participants needed significantly more steps to complete an obstacle course when walking with the Rheo Knee(R) II compared to the non-microprocessor controlled prosthetic knee (median [interquartile range] resp. 23.50 [19.92-26.25] and 22.17 [19.50-25.75]; P=0.041). On other outcome measures, no significant differences were found.
Conclusions: Transition towards the Rheo Knee(R) II had little effect on the studied outcome measures.

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6. Changes in Strength, Sensation, and Prehension in Acute Cervical Spinal Cord Injury: European Multicenter Responsiveness Study of the GRASSP
Velstra IM, Curt A, Frotzler A, Abel R, Kalsi-Ryan S, Rietman JS, Bolliger M

Objective: To investigate the internal and external responsiveness and recovery profiles of the Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) instrument in revealing changes in upper limb function within the first year following cervical spinal cord injury (SCI).
Method: A European prospective, longitudinal, multicenter study assessing the GRASSP at 1, 3, 6, and 12 months after cervical SCI. Subtests of GRASSP were compared to the upper extremity motor (UEMS) and light touch scores (LT) according to the International Standards of Neurological Classification of Spinal Cord Injury (ISNCSCI), the Spinal Cord Independence Measure self-care subscore (SCIM-SS), as well as a clinician-rated outcome measure (CROM) of clinical relevance. Data were analyzed for GRASSP responsiveness and recovery rate over time.
Results: Seventy-four participants entered the study. GRASSP subtests proved responsive (standardized response mean [SRM] ranged from 0.79 to 1.48 for strength, 0.50 to 1.03 for prehension, and 0.14 to 0.64 for sensation) between all examination time points. In comparison, UEMS and LT showed lower responsiveness (SRM UEMS ranged from 0.69 to 1.29 and SRM LT ranged from 0.30 to -0.13). All GRASSP subtests revealed significant, moderate-to-excellent correlations with UEMS, LT, and SCIM-SS at each time point, and changes in GRASSP subtests were in accordance with the CROM. GRASSP prehension and motor recovery was largest between 1 and 3 months.

Conclusion: The GRASSP showed excellent responsiveness, detecting distinct changes in strength and prehension relating to the severity of cervical SCI. It detected clinically significant changes complimentary to the ISNCSCI and SCIM-SS assessments.

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Totale impact factor: 10.780
Gemiddelde impact factor: 2.695

Thoraxchirurgie

1. Off-pump no-touch technique: 3-year results compared with the SYNTAX trial
Arrigoni SC, Mecozzi G, Grandjean JG, Hillege JL, Kappetein AP, Mariani MA

Objectives: A 3-year follow-up of a retrospective, single-centre clinical study of OPCAB (off-pump coronary artery bypass) no-touch technique with arterial composite grafts and an indirect comparison with clinical outcomes of the 3-year follow-up of the SYNTAX trial.
Methods: A total of 400 consecutive patients ('all-comers') who underwent OPCAB no-touch coronary surgery. Primary endpoint was 3-year MACCE (major adverse cardiovascular and cerebrovascular events). These results were compared with the randomized arms of the SYNTAX trial.
Results: The observed 3-year survival was 82.2%. The cumulative 3-year freedom from MACCE was 89.7%. The percentage of MACCE was significantly lower ($P < 0.001$) in the OPCAB no-touch group (10.3%) compared with both arms of the SYNTAX trial (20.2 and 28.0%, respectively). Repeat revascularization in the OPCAB no-touch group (4.3%) was significantly lower ($P < 0.001$) compared with both arms of the SYNTAX trial (10.7 and 19.7%, respectively). The percentage of stroke was significantly lower ($P = 0.032$) in the OPCAB no-touch group compared with the CABG arm in the SYNTAX trial (1.3 vs 3.4%). There was no significant difference of stroke rate between the OPCAB no-touch group and the PCI arm of the SYNTAX trial (1.3 vs 2%, $P = 0.347$).
Conclusions: The results at the 3-year follow-up showed the safety and efficacy of OPCAB no-touch technique. The OPCAB no-touch technique may improve patients' outcome by minimizing the morbidity and the neurological complications. Prospective controlled trials are needed to confirm these results.

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2. C4b-Binding Protein Deposition is Induced in Diseased Aortic Heart Valves, Coinciding with C3d
Dikhoff MJ, ter Weeme M, Vonk AB, Kupreishvili K, Blom AM, Krijnen PA, Stooker W, Niessen HW

Background and aim of the study: It has been found recently that activated complement is more widespread in diseased aortic valves compared to the endogenous complement inhibitors C1-inhibitor and clusterin. Previously, another endogenous inhibitor of complement, C4b-binding protein (C4BP) has been described in atherosclerotic diseased coronary arteries. The study aim was to analyze C4BP levels in diseased aortic valves.
Methods: Aortic valve tissue was derived from surgical procedures and classified as 'degenerative', 'atherosclerotic' or 'atherosclerotic with bacterial infection'. Valves

were stained with specific antibodies against C4BP, C3d and caspase-3. Areas of positivity were then quantified using computer- assisted morphometry.
Results: In atherosclerotic valves, the areas of C4BP and C3d positivity (38.8 +/- 0.4% versus 32.7 +/- 1.0%, respectively) were significantly higher compared to the degenerative and control groups. In atherosclerotic valves with bacterial infection, the area of positivity for C4BP was even further increased compared to atherosclerotic valves (65.1 +/- 1.2%; 70.1 +/- 1.9% for C3d). The areas of C4BP and C3d positivity were not significantly different in all groups. Caspase-3 was only present in <10% of endothelial cells in the atherosclerotic valves without bacterial infection and in neutrophilic granulocytes in atherosclerotic valves, with and without bacterial infection.
Conclusion: It has been shown for the first time that C4BP is deposited in the diseased aortic valve, coinciding with C3d. The area of C4BP positivity was more extensive compared to the areas of other endogenous complement inhibitors (C1-inhibitor and clusterin).

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