# Wetenschappelijk onderzoek in Medisch Spectrum Twente

# 2017

# Inhoudsopgave

# Voorwoord

Voor u ligt de negende editie van het jaarlijkse overzicht van het wetenschappelijk overzicht wat door medewerkers van Medisch Spectrum Twente in 2017 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 2017 zijn. De zogenaamde “Epub Ahead of Print” artikelen komen in de volgende uitgave. Daarnaast worden ook peer-reviewed artikelen uit Nederlandstalige tijdschriften opgenomen.

In 2017 zijn 216 unieke publicaties verschenen in peer-reviewed tijdschriften. Dit is over de afgelopen 5 jaar gekeken ongeveer gemiddeld. De gemiddelde impact score van alle artikelen is 4,47 wat ook gemiddeld is. Dit jaar hebben we voor het eerst in vele jaren helaas niet in de absolute toptijdschriften Lancet en New England Journal of Medicine gepubliceerd. Wel twee keer in Lancet subjournals.

Qua promoties was 2017 een matig jaar met maar 4 promoties in MST.

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

Om de ontwikkeling te kunnen volgen zijn de ranglijsten van 2017 naast die van eerdere jaren weergegeven.

Ik wens u veel leesplezier toe,

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# Overzicht publicaties en de Top 3

| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|---|---|
| Unieke publicaties | 109 | 177 | 190 | 213 | 191 | 212 | 245 | 226 | 216 |
| Impact factor | 3,16 | 5,12 | 3,63 | 3,97 | 4,38 | 4,03 | 5,06 | 4,70 | 4,47 |

| | 2014 | | 2015 | | 2016 | | 2017 | |
|---|---|---|---|---|---|---|---|---|
| **Top 3: Aantal publicaties:** | | | | | | | | |
| 1 | Neurologie | 39 | Medical School | 35 | Neurologie | 41 | Cardiologie | 31 |
| 2 | Medical School | 33 | Neurologie | 33 | Cardiologie | 39 | Heelkunde | 30 |
| 3 | Cardiologie | 25 | Heelkunde | 31 | Medical School | 33 | Neurologie | 28 |
| **Top 3: Totale impact factor score:** | | | | | | | | |
| 1 | Cardiologie | 149 | Neurologie | 184 | Cardiologie | 251 | Cardiologie | 181 |
| 2 | Neurologie | 110 | Heelkunde | 178 | Neurologie | 170 | Neurologie | 136 |
| 3 | Reumatologie | 107 | Cardiologie | 141 | Medical School | 135 | Heelkunde | 116 |
| **Top 3: Gemiddelde impact factor score:** | | | | | | | | |
| 1 | MDL | 6.1 | Gynaecologie | 12.5 | Gynaecologie | 16.7 | Klin. Chemie | 6.9 |
| 2 | Pathologie | 6.0 | MDL | 11.8 | Radiotherapie | 8.2 | Radiotherapie | 6.7 |
| 3 | Cardiologie | 6.0 | Klin. chemie | 10.5 | Klin. Chemie | 6.9 | Interne gnkd | 6.1 |
| **Top 3: Aantal publicaties als 1e, 2e of laatste auteur:** | | | | | | | | |
| 1 | Neurologie | 22 | Neurologie | 17 | Cardiologie | 18 | Cardiologie | 14 |
| 2 | Medical School | 18 | Medical School | 16 | Medical School | 16 | Longziekten | 14 |
| 3 | Cardiologie | 15 | Cardiologie | 15 | Neurologie | 14 | Heelkunde | 11 |
| | Reumatologie | 15 | Heelkunde | 15 | | | | |
| **Top 3: Totale impact factor score als 1e, 2e of laatste auteur:** | | | | | | | | |
| 1 | Cardiologie | 98 | Cardiologie | 65 | Cardiologie | 110 | Cardiologie | 63 |
| 2 | Neurologie | 52 | Neurologie | 48 | Longziekten | 57 | Neurologie | 39 |
| 3 | Medical School | 51 | Reumatologie | 46 | Neurologie | 47 | Longziekten | 37 |
| **Top 3: Gemiddelde impact factor score als 1e, 2e of laatste auteur:** | | | | | | | | |
| 1 | Cardiologie | 6.5 | Gynaecologie | 6.0 | Cardiologie | 6.1 | Gynaecologie | 4.6 |
| 2 | Intensive Care | 6.1 | Pathologie | 5.6 | Longziekten | 5.1 | Cardiologie | 4.6 |
| 3 | MDL | 4.7 | Intensive Care | 5.4 | Microbiologie | 4.4 | Neurologie | 3.9 |

# Overzicht aantal publicaties per vakgroep:

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

# Promoties in MST in 2017
# **Cardiologie**

## Second-generation drug-eluting

## Stents and beyond

Dissertation

to obtain the degree of doctor at the University of Twente
on the authority of the rector magnificus,
Prof. dr. T.T.M. Palstra,
on account of the decision of the graduation committee,
to be publicly defended
on Wednesday 6 December 2017 at 16.45

by

**Liefke Clementine van der Heijden**

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**Samenvatting**

Medicijn-afgevende stents (drug-eluting stents; DES) zijn onmisbaar geworden voor de behandeling van coronair lijden. Er vinden continu ontwikkelingen plaats om de veiligheid en effectiviteit van deze stents te optimaliseren. De tweede generatie DES zijn ten opzichte van de eerste generatie DES verbeterd op het gebied van biocompatibiliteit, waardoor zij minder invloed hebben op de inductie van een inflammatoire respons in de vaatwand. Bij de nieuwe-generatie stents is de flexibiliteit van de stent platforms verbeterd, waardoor de plaatsbaarheid en de hechting van de stents aan de vaatwand aanzienlijk is verbeterd. Dit kan voornamelijk van voordeel zijn bij de behandeling van coronair lijden waarbij er sprake is van een uitdagende anatomie en/of complexe laesies.

Terwijl de korte-termijn follow-up van tweede- en nieuwe generatie stents goed zijn onderzocht in gerandomiseerde studies in een brede groep van patiënten, is er nog onvoldoende informatie beschikbaar over de lange termijn veiligheid en effectiviteit van deze stents. Daarnaast is er nog weinig bekend over de prestaties van nieuwe-generatie DES bij patiënten met complexe laesies.

Dit proefschrift evalueert de impact van verschillende stents op de klinische uitkomst in zowel een algemene patiënten populatie als in patiënten die complexe laesies hebben. Daarnaast zullen nieuwe types stents, zoals stents met biologisch afbreekbare polymeren, geheel oplosbare scaffolds en de COMBO stent die van een nieuwe soort technologie gebruik maakt bediscussieerd worden. **Hoofdstuk 1** geeft een korte samenvatting over de ontwikkelingen van DES en de voordelen die tweede- en nieuwe-generatie DES op klinische uitkomst kunnen hebben. Daarnaast wordt laten zien dat het interessant is om de impact van de geïmplanteerde stent op de klinische uitkomst te onderzoeken in hoog-risico patiënten en patiënten met complexe laesies.

**Deel II: Onderzoek in brede patiënten populaties**

**Hoofdstuk 2** laat de 5-jaar follow-up zien van de gerandomiseerde TWENTE trial, waarbij de veiligheid en effectiviteit van twee nieuwe-generatie DES zijn vergeleken. Daarnaast zijn de lange termijn uitkomsten van patiënten die geschikt waren voor deelname aan de TWENTE trial, maar die niet geïncludeerd zijn onderzocht. In totaal zijn 1,391 patiënten geïncludeerd in de TWENTE trial. De incidentie van het primaire eindpunt “target vessel failure”, een gecombineerd eindpunt bestaande uit cardiale dood, myocard infarct en target vessel-gerelateerde revascularisatie, was gelijk onder patiënten die met de zotarolimus-afgevende stent versus de everolimus-afgevende stent behandeld werden (16.1% vs. 18.1%). Definitieve stent trombose kwam bij beide stents weinig voor. Target vessel failure kwam vaker voor onder de 318 patiënten die niet geïncludeerd, maar wel geschikt waren voor inclusie. Als je de populatie van deelnemers aan de TWENTE trial en de niet-geïncludeerden bij elkaar optelt, dan was het totale percentage target vessel failure slechts licht verhoogd

vergeleken met het percentage target vessel failure bij alleen de deelnemers van de TWENTE trial optrad (18.3% vs. 17.1%). De lange termijn uitkomsten van de niet-geïncludeerde patiënten bevestigt de validiteit van de gerandomiseerde trial en representeert samen met de studie resultaten een sterk argument voor lange termijn veiligheid van de tweede-generatie DES die gebruikt zijn.

**Hoofdstuk 3** presenteert data betreffende de driejaars veiligheid en effectiviteit van stent plaatsing met nieuwe generatie zotarolimus-afgevende Resolute Integrity en everolimus-afgevende Promus Element stents in de gerandomiseerde DUTCH PEERS trial. Van alle 1,811 patiënten die geïncludeerd zijn in de DUTCH PEERS trial is driejaars follow-up beschikbaar in 1,807 (99.8%) patiënten. Na drie jaar follow-up is het optreden van target vessel failure gelijk voor beide stentgroepen (10.7% vs. 10.3%). Bij de verschillende componenten van het gecombineerde eindpunt target vessel failure wordt ook geen verschil gezien, evenals dat er geen verschil wordt gezien in het percentage definitieve-of-waarschijnlijke stent trombose. Dit hoofdstuk laat zien dat nieuwe generatie Resolute Integrity en Promus Element stents veilig en effectief zijn voor het behandelen van obstructief coronair lijden in een all-comer patiënten populatie.

**Hoofdstuk 4** evalueert de klinische uitkomsten na drie jaar bij patiënten van de DUTCH PEERS trial die een verhoogd risico hebben op nadelige klinische uitkomsten. Patiënten vallen onder de hoog-risico categorie als ze aan tenminste één van de volgende voorwaarden voldoen: (1) diabetes mellitus, (2) myocard infarct in de voorgeschiedenis, (3) coronaire revascularisatie in de voorgeschiedenis, (4) chronische nierinsufficiëntie, (5) linker ventriculaire ejectie fractie ≤30%, of (6) leeftijd ≥75 jaar. Van alle 1,811 gerandomiseerde patiënten in de DUTCH PEERS trial kunnen 957 (52.8%) als hoog-risico patiënten geclassificeerd worden. De 3-jaars incidentie van het gecombineerde eindpunt target vessel failure is hoger in hoog-risico patiënten dan in patiënten met een laag-tot-intermediair risico (13.2%vs. 7.5%). De veiligheid en effectiviteit van de nieuwe generatie Resolute Integrity en Promus Element stents in hoog risico patiënten is vergelijkbaar (target vessel failure 13.3% vs. 13.1%).

**Hoofdstuk 5** beschrijft een propensity score gematchte analyse waarin de COMBO stent met een gecombineerde populatie van patiënten vergeleken is die behandeld waren met de nieuwe generatie Resolute Integrity en Promus Element stents. De COMBO stent combineert een abluminale, sirolimus-afgevende laag met een luminale endotheel progenitorcel-bevattende laag, wat als doel heeft om herstel van de vaatwand na stentplaatsing te bevorderen. Na propensity score matching is een populatie van 771 patiënten die behandeld zijn met de COMBO stent en 771 patiënten die behandeld zijn met de Resolute Integrity of Promus Element stent met

elkaar vergeleken. Twee jaar follow-up toont geen significant verschil in target laesie failure tussen beide groepen (7.9% vs. 6.4%). Definitieve stent trombose is ook vergelijkbaar tussen beide groepen (0.8% vs. 0.7%). Dit hoofdstuk laat zien dat, in dit gematchte cohort, geen significant verschil in klinische uitkomst is geobserveerd tussen patiënten behandeld met de COMBO stent versus patiënten behandeld met nieuwe generatie Resolute Integrity of Promus Element DES.

**Hoofdstuk 6** toont de 1 jaar follow-up van de BIO-RESORT trial. De BIO-RESORT trial is een onderzoeker geïnitieerde, multicenter, gerandomiseerde trial met als doel de veiligheid en effectiviteit van twee nieuwe DES met biologisch afbreekbare polymeer coatings (sirolimus-afgevende Orsiro stent en everolimus-afgevende Synergy stent) te vergelijken met de nieuwe-generatie Resolute Integrity stent met permanente polymere coating. Na 1-jaar follow-up zijn beide biologisch afbreekbare polymeer coating stents niet-inferieur aan de Resolute Integrity stent. Dat er na 1 jaar geen verslechterde veiligheid en effectiviteit gezien wordt is een belangrijk feit voordat de mogelijke lange termijn voordelen van deze stents onderzocht worden.

**Hoofdstuk 7** evalueert de veiligheid en effectiviteit van de Absorb biologisch afbreekbare vasculaire scaffold na één jaar follow-up. Deze scaffold is ontwikkeld met de gedachte de lange-termijn veiligheidsaspecten van metalen DES te verbeteren. Echter, deze meta-analyse laat zien dat gedurende het eerste jaar van follow-up de patiënten die behandeld zijn met biologisch afbreekbare scaffolds een hogere incidentie hebben van myocard infarcten en scaffold trombose in vergelijking tot patiënten die met everolimus-afgevende stents met permanente polymeren behandeld zijn. Aangezien het voordelige effect van de scaffold mogelijk pas op de langere termijn zichtbaar is, is toekomstige lange-termijn follow-up van deze scaffold erg belangrijk.

**In hoofdstuk 7.1** discussiëren we over de mogelijke mechanismen van trombose van biologisch afbreekbare vasculaire scaffolds. Wij concluderen dat, gezien het feit dat het mechanisme van scaffold trombose nog niet volledig begrepen wordt en moderne metalen DES excellente uitkomsten laten zien in all-comers, biologische afbreekbare scaffolds bij voorkeur alleen gebruikt zouden moeten worden in klinische trials.

**Hoofdstuk 8** introduceert de rationale en studie design van de BIONYX trial. De BIONYX trial is een onderzoek geïnitieerde, internationale, multicenter, gerandomiseerde klinische studie. Patiënten van 7 studiecentra uit Nederland, België en Israël zullen worden gerandomiseerd (1:1, gestratificeerd voor geslacht en diabetes mellitus) naar behandeling met de nieuwste-generatie zotarolimus-afgevende permanente polymeer-coating Resolute Onyx stent of naar behandeling met de sirolimus-afgevende biologisch afbreekbare polymeer-coating Orsiro stent.

Terwijl beide stents al gebruikt worden voor de behandeling van diverse patiënten met verschillende soorten laesies, is er nog nooit een vergelijking uitgevoerd tussen deze beide stents. De doelstelling van de BIONYX trial is dan ook te onderzoeken of de veiligheid en effectiviteit na 1 jaar vergelijkbaar is in een all-comer patiënten populatie die behandeld wordt met de permanent polymeer-coating Resolute Onyx stent versus de biologisch afbreekbare polymeer-coating Orsiro stent (als referentie).

**Deel III: Medicijn-afgevende stents voor de behandeling van complexe laesies**
**Hoofdstuk 9** onderzoekt een opeenvolgende serie aan patiënten die vanwege stabiele angina pectoris of een niet-ST-elevatie myocard infarct een PCI hebben ondergaan met plaatsing van een tweede-generatie DES. Het doel is om de impact van een coronaire bypass operatie (CABG) in de voorgeschiedenis te bepalen op de 5-jaar uitkomst na PCI. Van alle 1,709 patiënten die hebben meegedaan aan de TWENTE trial en die niet geïncludeerd zijn maar gevolgd zijn in de non-enrolled TWENTE registratie, hebben 202 (11.8%) patiënten een CABG in de voorgeschiedenis. Cardiale dood (10.4% vs. 4.3%) en target vessel revascularisaties (25.0% vs. 8.1%) treden na 5-jaar vaker op bij patiënten met een bypass operatie in de voorgeschiedenis. Deze verschillen blijven bestaan nadat er voor verschillen in patiënt- en laesie karakteristieken is gecorrigeerd. Target vessel revascularisatie kwam het vaakst voor in patiënten die een PCI ondergingen van een venegraft. Wetenschap over de veiligheid, maar het verhoogde risico op herhaalde revascularisaties bij patiënten met een bypass operatie in de voorgeschiedenis die een PCI ondergaan is belangrijk voor cardiologen en andere medici betrokken bij het hartteam en is belangrijk voor de informed consent procedure.

**Hoofdstuk 10** geeft data weer van de klinische uitkomsten twee jaar na behandeling van bifurcatielaesies in een all-comer patiënten populatie van de DUTCH PEERS trial, allen behandeld met nieuwe-generatie DES. Van alle 1,811 patiënten die geïncludeerd waren in de trial hebben 465 (25.7%) ten minste één bifurcatielaesie waarvoor zij behandeld zijn. De incidentie van target vessel failure was gelijk voor patiënten met – en patiënten zonder bifurcatielaesies. Target vessel myocard infarcten kwamen vaker voor in de bifurcatie-groep (3.5% vs. 1.6%). Na multivariate analyse bleek echter dat behandeling van een bifurcatie laesie geen onafhankelijk voorspeller voor het optreden van target vessel myocard infarcten was. Als alleen naar de groep patiënten gekeken werd die voor ten minste één bifurcatielaesie behandeld werden, dan was er geen impact van type DES, het formaat van de zijtak, of het wel of niet gebruiken van kissing-balloon inflatie op diverse klinische eindpunten. Periprocedureel myocard infarct kwam vaker voor bij patiënten die met twee stents behandeld werden ten opzichte van patiënten die met één stent behandeld werden. Onze bevindingen suggereren dat de flexibele nieuwe-generatie DES veilig en effectief zijn voor de behandeling van bifurcatielaesies.

**Hoofdstuk 11** laat de impact zien van een echte bifurcatie laesie op 3-jaar klinische uitkomst. Echte bifurcatielaesies zijn laesies waarbij zowel het hoofdvat als het zijvat aangedaan zijn. Patiënten die met tweede-generatie stents behandeld werden voor echte bifurcatie-laesies (n=115) hadden een wat hoger percentage events dan patiënten die behandeld werden voor niet-echte bifurcatielaesies (n=171). Dit verschil was echter niet statistisch significant (20.0% vs. 11.7%). Tot aan 3-jaar follow-up was het merendeel van de patiënten in beide groepen vrij van klachten van pijn op de borst.

**Hoofdstuk 12** evalueert de hypothese dat patiënten die een bifurcatielaesie hebben en behandeld worden met een nieuwe-generatie DES, een hoger percentage events hebben als er ook nog sprake is van een ernstige calcificatie in die bifurcatielaesie. Om deze hypothese te toetsen hebben we alle patiënten van de TWENTE en DUTCH PEERS trials die voor tenminste één bifurcatie laesie behandeld werden onderzocht. Van de 827 patiënten met een bifurcatie laesie hadden 168 (20.3%) van de patiënten tevens ernstige calcificaties in de bifurcatie laesie. Patiënten met ernstige calcificaties waren ouder, hadden vaker diabetes mellitus en de laesies werden vaker voorbehandeld tijdens de PCI procedure. Het samengestelde eindpunt target vessel failure was niet significant verschillend na 2-jaar tussen beide groepen (11.9% vs. 10.2%). Het percentage definitieve-of-waarschijnlijke stent trombose was ook laag en gelijk (0.6% vs. 0.9%). Dit hoofdstuk laat zien dat de aanwezigheid van ernstige calcificatie van de bifurcatie laesie geen significante verhoging gaf van het risico op nadelige events bij patiënten die met nieuwe-generatie DES behandeld zijn.

**Hoofdstuk 13** geeft inzicht in de impact van het behandelen van kleine vaten op resultaten na 2-jaar bij patiënten die behandeld zijn met nieuwe-generatie DES. Van de 1,811 deelnemers aan de DUTCH PEERS trial zijn 798( 44.1%) van de patiënten behandeld in tenminste één klein vat (diameter <2.50 mm). Het gecombineerde eindpunt target laesie falen was significant hoger bij patiënten die in tenminste één klein vat behandeld werden. Multivariate analyse met propensity score correctie laat zien dat het behandelen van een klein vat een onafhankelijk voorspeller is voor het optreden van target laesie falen na 2-jaar follow-up (hazard ratio 1.60). Patiënten behandeld met Resolute Integrity stents en patiënten behandeld met Promus Element stents ervaren even vaak target laesie falen (9.9% vs. 9.1%). Patiënten die het kleinst behandelde vat <2.25 mm hebben, hebben een vergelijkbaar aantal events als patiënten met het kleinst behandelde vat tussen de 2.25 en 2.50 mm. Patiënten die in vaten behandeld worden die niet kleiner zijn dan 2.50 tot <3.00 mm en patiënten die enkel behandeld worden in vaten ≥3.00 mm hebben minder vaak target lesion failure. Deze data suggereren dat bij gebruik van nieuwe-generatie DES, een vaatdiameter van <2.50 mm een goed afkappunt zou kunnen zijn om een klein vat te definiëren.

**Hoofdstuk 14** onderzoekt de impact van ernstige laesie calcificaties op de klinische uitkomst bij patiënten die zich presenteren met stabiele angina pectoris en een PCI ondergaan met plaatsing van een nieuwe-generatie DES. Van alle patiënten van de TWENTE en DUTCH PEERS trial zijn in totaal 1,423 patiënten behandeld voor stabiele angina pectoris. Van deze patiënten hebben 342 (24.0%) ernstige calcificaties in tenminste één laesie. Na 2-jaar follow-up, is de incidentie target vessel falen significant hoger in de groep die tenminste één ernstige laesie calcificatie had (25.7% vs. 20.4%). Multivariate analyse laat zien dat ernstige laesie calcificatie een onafhankelijke voorspeller is van het optreden van het primaire eindpunt target vessel falen na 2-jaar follow-up. Het verschil komt voort uit een verschil in het eerste jaar. De informatie over de resultaten van PCI met nieuwe-generatie DES bij patiënten met ernstige laesie calcificaties kan meegenomen worden bij het maken van therapeutische beslissingen.

**Hoofdstuk 15** beschrijft de invloed van ernstige calcificaties bij patiënten van de TWENTE en DUTCH PEERS trial die zich presenteren met een acuut coronair syndroom waarvoor ze behandeld worden met nieuwe-generatie DES. Van de 1,779 patiënten met een acuut coronair syndroom hebben 340 (19.1%) een behandeling ondergaan in tenminste één ernstig gecalcificeerde laesie. Target vessel falen kwam vaker voor bij patiënten met ernstige laesie calcificaties (12.4% vs. 7.0%). Multivariate analyse laat zien dat ernstige laesie calcificatie een onafhankelijke voorspeller is voor het optreden van target vessel falen. Dit hoofdstuk laat zien dat, ondanks de verbeteringen in DES, de aanwezigheid van ernstige calcificaties nog steeds een voorspeller is van een slechtere uitkomst.

**Hoofdstuk 16** evalueert in een gepoolde database van deelnemers aan de TWENTE en DUTCH PEERS trials de impact van het type stent dat gebruikt is (Xience V versus Promus Element) op 3-jaar klinische uitkomst bij patiënten met ernstige calcificaties. De Promus Element stent maakt gebruik van dezelfde coating als de Xience V stent, maar heeft een nieuw flexibel stent design gemaakt van platinum-chromium, waardoor de radiale kracht en de angiografische zichtbaarheid van deze stent moet zijn verbeterd. Na 3-jaar follow-up wordt gezien dat er na behandeling met de Promus Element stent minder vaak target vessel myocard infarcten op getreden zijn dan na behandeling met Xience V stents (2.0% vs. 9.1%). Na propensity score correctie is gebruik van de Promus Element nog steeds geassocieerd met een lager risico op target vessel gerelateerde myocard infarcten. Wat betreft cardiale dood en aantal revascularisaties wordt er geen verschil gezien tussen beiden. Dit hoofdstuk laat zien dat bepaalde stents mogelijk een hoger risico op nadelige uitkomsten kan laten zien in bepaalde hoog risico groepen, terwijl de stents wel veilig en effectief gevonden zijn in een brede patiëntenpopulatie met verschilende type laesies.

**Hoofdstuk 17** bediscussiëren we kort de bevindingen van dit proefschrift en geven we de toekomst-perspectieven weer.

**Conclusies**
Medicijn-afgevende stents worden veel gebruikt in de dagelijkse klinische praktijk. Er vinden continu ontwikkelingen plaats van deze stents om de klinische uitkomst te verbeteren. De tweede-generatie stents en de nieuwe-generatie stents hebben in termen van veiligheid en effectiviteit beide uitstekende uitkomsten laten zien op zowel de korte- als de lange-termijn follow-up. Door lage hoeveelheden events wordt het moeilijk om voordeel aan te tonen van nieuwe ontwikkelingen van stents boven de al bestaande stents. Om toch voldoende statistische power te bereiken kan het daarom interessant zijn om de focus van het onderzoek te leggen op hoog-risico patiënten of patiënten met complexe laesies. Het is mogelijk om hoog-risico patiënten te definiëren op basis van eerdere studies. In de gerandomiseerde DUTCH PEERS trial wordt laten zien dat volgens die definitie hoog-risico patiënten inderdaad vaker target vessel failure hebben na 3-jaar follow-up, zonder dat er verschil was tussen de twee nieuwe-generatie stents. De klinische uitkomst bleek niet verschillend te zijn tussen patiënten die wel of niet voor bifurcatielaesies behandeld werden. Wel bleek dat patiënten met een bypass operatie in de voorgeschiedenis, patiënten die behandeld zijn in tenminste één klein vat (<2.50 mm) en patiënten die in tenminste één van de behandelde laesies ernstige calcificaties had zitten een hoger risico op adverse event hebben dan patiënten die dit niet hadden. Een sub-analyse van de op patiënten niveau gepoolde data van de TWENTE en DUTCH PEERS trial laat zien dat bij patiënten die behandeld zijn met de nieuwe generatie Promus Element stent na 3-jaar follow-up minder vaak een target vessel myocard infarct geobserveerd werd dan bij patiënten die behandeld zijn met de tweede-generatie Xience V stent. Andere uitkomsten zijn niet verschillend tussen beide groepen. Omdat dit een propensity-score gecorrigeerde analyse is en niet een gerandomiseerde studie, moeten de resultaten met enige voorzichtigheid geïnterpreteerd worden en kan de conclusie alleen als hypothese genererend gezien worden. Echter suggereren deze wel dat het waardevol zou kunnen zijn om potentiële voordelen van nieuwe stent-ontwikkelingen te onderzoeken in een subgroep van patiënten met een hoog risico. Naast de ontwikkeling van de permanente polymere coatings DES zijn er nu ook stents met biologisch afbreekbare polymere coatings ontwikkeld. In de BIO-RESORT wordt gezien dat na één jaar behandeling met twee nieuwe biologisch afbreekbaar polymeer-coating stents non-inferieur is gebleken aan behandeling met de nieuwe generatie Resolute Integrity stent in een all-comer patiënten populatie. Voordat mogelijke lange termijn voordelen van deze stents onderzocht worden is het belangrijk de veiligheid en effectiviteit na 1-jaar te beschrijven.

De laatste ontwikkeling die plaatsgevonden heeft is de ontwikkeling van biologisch afbreekbare vasculaire scaffolds. Doelstelling van deze scaffolds is om te voorkomen dat er levenslang een device in het coronaire vat aanwezig blijft. Onze meta-analyse laat zien dat gedurende het eerste jaar follow-up er een significant hoger percentage myocard infarcten en scaffold tromboses optreedt bij patiënten die met een biologisch afbreekbare scaffold behandeld worden ten opzichte van patiënten die met een permanente metalen DES behandeld worden. De mechanismen achter scaffold trombose moeten nog verder onderzocht worden. Moderne DES hebben uitstekende resultaten laten zien, waaronder een laag percentage stent trombose, bij zowel all-comer patiënten populaties als in hoog-risico patiënten groepen. Het is daarom redelijk om te suggereren dat het gebruik van de huidige generatie biologisch oplosbare scaffolds bij voorkeur beperkt zou moeten worden tot klinische studies.

# Cardiologie

## Peripheral endothelial function after ST-segment elevation myocardial infarction

Dissertation

to obtain
the degree of doctor at the University of Twente,
on the authority of the rector magnificus,
Prof. dr. T.T.M. Palstra,
on account of the decision of the graduation committee,
to be publicly defended
on Wednesday 6 December 2017 at 14.45 hrs

by

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**Samenvatting**
Hart- en vaatziekten zijn doodsoorzaak nummer 2 in Nederland. De ischemische hartziekten en de beroerten zijn verantwoordelijk voor ongeveer de helft van alle hart- en vaatziekten. Door verbeteringen in cardiovasculaire preventie en medische behandeling zijn de sterftecijfers van ischemische hartziekten, en vooral die van het hartinfarct, verminderd. Desondanks zal, door de verwachte vergrijzing in ons land, het absolute aantal patiënten met ischemische hartziekten verder toenemen.

Een goed functionerend endotheel, de belangrijkste regulator van de bloedstroom, is van belang voor een goed arterieel vaatbed. Endotheel dysfunctie speelt dan ook een centrale rol bij de ontwikkeling van atherosclerose (aderverkalking). Atherosclerotische plaques, die daarbij gevormd worden, kunnen tijdens lichamelijke inspanning klachten van pijn op de borst veroorzaken of ze kunnen leiden tot een acuut coronair syndroom. Het ernstigste type hiervan is het hartinfarct (ST-elevatie myocardinfarct (STEMI)), dat doorgaans wordt behandeld door middel van een primaire percutane coronaire interventie (PPCI). Op de lange termijn kunnen echter opnieuw cardiovasculaire aandoeningen optreden. De vroege identificatie van patiënten met endotheel dysfunctie kan het optreden van belangrijke complicaties van atherosclerose verminderen door cardiovasculaire risicofactoren onder strikte controle te houden. Aangezien de perifeer gemeten endotheel functie een goede afspiegeling is van de coronaire endotheel functie, kan niet-invasief gemeten perifere endotheel functie gebruikt worden als surrogaat voor de coronaire endotheel functie.

Bij patiënten met bekende cardiovasculaire risicofactoren of milde atherosclerotische aandoeningen is de relevantie van het detecteren van endotheliale dysfunctie voor risicobeoordeling aangetoond. Het was echter onduidelijk of kennis over de endotheel functie nuttig is bij patiënten die al een STEMI hebben gehad. Gegevens ontbraken over zowel het beloop van de endotheel functie als de relatie tussen de endotheel functie en klinische uitkomsten op de lange termijn. Dit leidde tot de volgende onderzoeksvragen: 1) is er een verband tussen endotheel functie en het wel of niet aantreffen van een open aangedane kransslagader ten tijde van de initiële coronaire angiografie bij patiënten met een hartinfarct; (2) is er een verband tussen endotheel functie en markers voor vaatontsteking; (3) is er een verbetering van endotheel functie na een STEMI als gevolg van leefstijlaanpassingen en medische behandeling, en; (4) is er een verband tussen endotheel functie na een STEMI en het optreden van cardiovasculaire aandoeningen op lange termijn. Dit proefschrift geeft de resultaten van het antwoord op bovenstaande onderzoeksvragen weer.

In **hoofdstuk 2** zijn de functie van het endotheel, de gevolgen van endotheel dysfunctie en verschillende methoden voor de detectie van endotheel dysfunctie beschreven. De focus is gelegd op de niet-invasieve beoordeling van de perifere

endotheel functie. Deze geeft in belangrijke mate weer hoe het gesteld is met de coronaire endotheel functie. Eerdere studies hebben gebruik gemaakt van ultrasound om de hyperemie geïnduceerde verwijding (Flow Mediated Dilatation FMD) van de bovenarmslagader te beoordelen als maat voor de perifere endotheel functie. Deze methode vereist echter enige opleiding en ervaring van degene die de metingen uitvoert, de operator. Een operator-onafhankelijk alternatief is de "reactive hyperemia peripheral arterial tonometry (RH-PAT)" methode. De technische achtergrond is beschreven als ook de resultaten van eerdere validatie studies. Een lage RH-PAT index geeft een slechte endotheel functie weer. Deze methode is gebruikt in dit proefschrift voor het meten van de endotheel functie.

In **hoofdstuk 3** is onderzocht in hoeverre de injectie van contrastvloeistof tijdens coronaire angiografie leidt tot verhoging van arteriële druk in de kransslagaders, die vervolgens de coronaire stroomsnelheid van het bloed zou kunnen versnellen - een onderzoeksvraag die zeer relevant is voor hoofdstuk 4. Er is na injectie een kleine toename van de arteriële druk. Deze is echter verwaarloosbaar en de coronaire bloedstroomsnelheid werd niet essentieel verhoogd. De beperkte invloed van contrastinjectie op intracoronaire bloeddruk bevestigt de waarde van de coronaire angiografie voor het schatten van de coronaire bloedstroomsnelheid.

In **hoofdstuk 4** is in 71 patiënten die zich presenteerden met een acuut hartinfarct onderzocht of degene met een open aangedane kransslagader een betere endotheel functie hadden dan patiënten bij wie de kransslagader dicht was ten tijde van de initiële coronaire angiografie (voorafgaande aan mechanische interventie). Patiënten die een open kransslagader, met een langzame of normale coronaire bloedstroom, hadden vóór PPCI, een significant (p=0,007) betere endotheel functie (RH-PAT-index 2,08 ± 0,34) dan patiënten met een dichte kransslagader (RH-PAT index 1,75 ± 0,35). Een betere endotheel functie was sterk en onafhankelijk geassocieerd met een open kransslagader. Zelfs na correctie voor leeftijd, geslacht en andere cardiovasculaire risicofactoren bleef dit verband overeind. Het tijdsinterval tussen het begin van de symptomen en PPCI, had ook geen invloed.

In **hoofdstuk 5** is in patiënten die recent een hartinfarct hadden doorgemaakt onderzocht of patiënten met hogere niveaus van twee laboratoriummarkers van vaatontsteking, namelijk hoog sensitief C-reactief proteïne (hs-CRP) en lipoproteïne geassocieerd fosfolipase $a_2$ (Lp-$PLA_2$) een endotheel dysfunctie hadden. Van de 11 patiënten met een hoog niveau van beide laboratoriummarkers had er 8 (72,7%) een endotheel dysfunctie (gedefinieerd als een RH-PAT-index <1,67), terwijl in de overige 57 patiënten er 26 (45,6 %) een endotheel dysfunctie hadden (p = 0,09). Bij patiënten met hoge niveaus van zowel hs-CRP en LpPLA,. bleek de endotheel functie gemiddeld enigszins lager te zijn dan in de overige patiënten, maar niet statistisch

significant lager (RH-PAT index 1,68 ± 0,22 vs 1,95 ± 0,63, p = 0, 17). Er was een aanzienlijke overlap tussen de RHPAT index metingen bij patiënten met versus zonder hoge niveaus van hs-CRP en Lp-PLA.

In **hoofdstuk 6** is de endotheel functie één maand (baseline), 6 maanden en 12 maanden na PPCI in 70 STEM/ patiënten, die optimale medische behandeling volgens de richtlijnen aangeboden kregen. Seriële endotheel functie gedurende een periode van een jaar na een recente STEM/ was tot nu toe nog niet eerder beschreven. De endotheel functie nam in de loop van de tijd af van een RH-PAT-index van 1,90 ± 0,58 bij de baseline, tot 1,81 ± 0,57 bij de follow-up van 6 maanden om uiteinde/ijkte dalen tot 1,69 ± 0,49 bij de follow-up van 12 maanden (p = 0,04 longitudinal mixed model). Meerdere cardiovasculaire risicofactoren bleken in de loop van de tijd te verslechteren: HbA1c; diastolische bloeddruk; totaal cholesterol; en LDL cholesterol. Geen van deze cardiovasculaire risicofactoren verantwoordelijk bleek te zijn voor de waargenomen afname van de endotheel functie door de tijd heen. De nieuwe bevindingen van deze studie suggereren dat endotheel dysfunctie uiteindelijk een stadium kan bereiken waarbij herstel onwaarschijnlijk of onmogelijk is, ondanks adequate of zelfs optimale medische behandeling. Andere factoren, zoals de totale belasting van de atherosclerotische plaque, genetische predispositie of andere nog onbekende risicofactoren, lijken in de loop van de tijd een belangrijke rol te spelen.

In **hoofdstuk 7** is onderzocht of de functie van het endotheel gemeten op baseline, cardiovasculaire aandoeningen tijdens langdurige follow-up kan voorspellen onder 70 patiënten met een recente STEM/. Totaal hadden 35 (50%) patiënten een endotheel dysfunctie, en 35 (50%) een normale endotheelfunctie. Periprocedurele "complicaties", zoals cardiogene shock of totaal atrioventriculaire blok, traden bij patiënten met een endotheel dysfunctie vaker op dan bij patiënten zonder endotheel disfunctie (25,7% versus 2,9%, p <0,01). Gedurende vier jaar follow-up kregen in totaal 20 (28,6%) patiënten een ernstige cardiovasculaire aandoening. Er was echter geen verband tussen de endotheel functie op baseline en het optreden van een cardiovasculaire aandoening gedurende de follow-up: 9 (25,7%) patiënten met een endotheel dysfunctie en 11 (31,5%) patiënten met normale endotheel functie kregen een cardiovasculaire aandoening (p = 0,52). Er was wel een duidelijk verband tussen de cardiovasculaire risicofactor diabetes mellitus en het optreden van cardiovasculaire aandoeningen. Zo heeft deze studie aangetoond dat de endotheel functie op baseline niet het risico op belangrijke nadelige cardiovasculaire aandoeningen kan voorspellen.

**Conclusie**

Alhoewel endotheel dysfunctie een belangrijke factor is in de ontwikkeling en progressie van atherosclerose, was het onduidelijk of gegevens over de endotheel functie nuttig zouden kunnen zijn bij patiënten die al een STEM! hebben gehad. We hebben geconstateerd dat bij patiënten met een acute STEM! een betere endotheel functie de kans op het aantreffen van een open aangedane kransslagader groter is dan het aantreffen van een dicht vat, voorafgaand aan elke mechanische interventie. Cardiovasculaire risicofactoren staan er om bekend dat ze zowel de endotheel dysfunctie als ontstekingsprocessen bevorderen die leiden tot de vorming van atherosclerotische laesies. Desalniettemin hebben we bij patiënten met een recente STEM! geen relatie gevonden tussen endotheel functie en ontstekingsmarkers. Seriële evaluatie van de endotheel functie toonde aan dat bij patiënten met een recente STEM! de endotheel functie niet verbeterde van baseline tot 12 maanden follow-up, ondanks de door de richtlijnen aanbevolen medische therapie. Onze gegevens suggereren dat de endotheel functie uiteindelijk een stadium kan bereiken, waarbij ondanks adequate of zelfs optimale medische behandeling en controle van risicofactoren, herstel onwaarschijnlijk is. Endotheel functie neemt af in de tijd. Bovendien bleek endotheel dysfunctie op baseline een significant verhoogde incidentie van periprocedurele "complicaties" te geven, maar konden cardiovasculaire aandoeningen tijdens een gemiddelde follow-up van 4 jaar niet worden voorspeld. Patiënten met diabetes mellitus op baseline hadden tijdens de follow-up een significant hogere kans op cardiovasculaire aandoeningen. Deze bevindingen impliceren dat bij STEMI-patiënten de totale omvang van veranderingen in de vaatwand en het aantal en de kwetsbaarheid van atherosclerotische laesies, die aanwezig zijn bij patiënten met diabetes, belangrijker lijken te zijn voor het algemene cardiovasculaire risico dan de mate van endotheliale dysfunctie.

# Interne Geneeskunde

Prediction and monitoring of chronic kidney disease

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van Rector Magnificus
prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
woensdag 7 juni 2017 om 11:00 uur

door

**Elise Schutte**

geboren op 7 augustus 1988 te
Vriezenveen

Promotores: Prof. dr. R.T. Gansevoort
Prof. dr. B.H.R. Wolffenbuttel
Prof. dr. H.J. Lambers Heerspink
Copromotor: Dr. H.L. Lutgers

Beoordelingscommissie:
Prof. dr. H.A.H. Kaasjager
Prof. dr. P.M. ter Wee
Prof. dr. J.L. Hillege

**Samenvatting**

Chronische nierschade (afgekort als CKD) wordt gedefinieerd als een verminderde nierfunctie of de aanwezigheid van tekenen van structurele nierschade die langer dan 3 maanden bestaan en de gezondheid beïnvloeden.[1] CKD komt voor bij ongeveer 10% van de wereldbevolking en vormt daarmee een substantiële belasting voor het mondiale welzijn.[2] CKD, en zijn belangrijkste veroorzakers hypertensie en diabetes mellitus, kunnen leiden tot eindstadium nierfalen, cardiovasculair lijden en sterfte.[1,3] Gezien de grote impact die CKD heeft op het mondiale welzijn is het nodig om factoren te identificeren die kunnen voorspellen of een patiënt met CKD ziekteprogressie zal doormaken omdat dit de patiënten zijn die nauwlettend moeten worden gevolgd en behandeld om hun risico op progressie te verlagen. Biomarkers worden vaak gebruikt als zo'n voorspellende factor. Een biomarker is een stof of eigenschap (bijvoorbeeld gewicht of temperatuur) die objectief gemeten en geëvalueerd kan worden en gebruikt kan worden als indicator van normale biologische processen, ziekteprocessen of farmacologische reacties op een therapeutische interventie.[4] Voor CKD zijn geschatte glomerulaire filtratiesnelheid (in dit hoofdstuk beschreven als nierfunctie) en aanwezigheid van albuminurie (eiwit in de urine) de belangrijkste biomarkers om het risico op het ontwikkelen van eindstadium nierfalen vast te stellen (Figuur 1).[1] Patiënten in de hoog-risico categorieën (veel albuminurie en/of een slechte nierfunctie) moeten behandeld worden om hun nierfunctieachteruitgang te vertragen, en daarmee zijn nierfunctie en albuminurie van groot belang in de dagelijkse praktijk van een nefroloog.

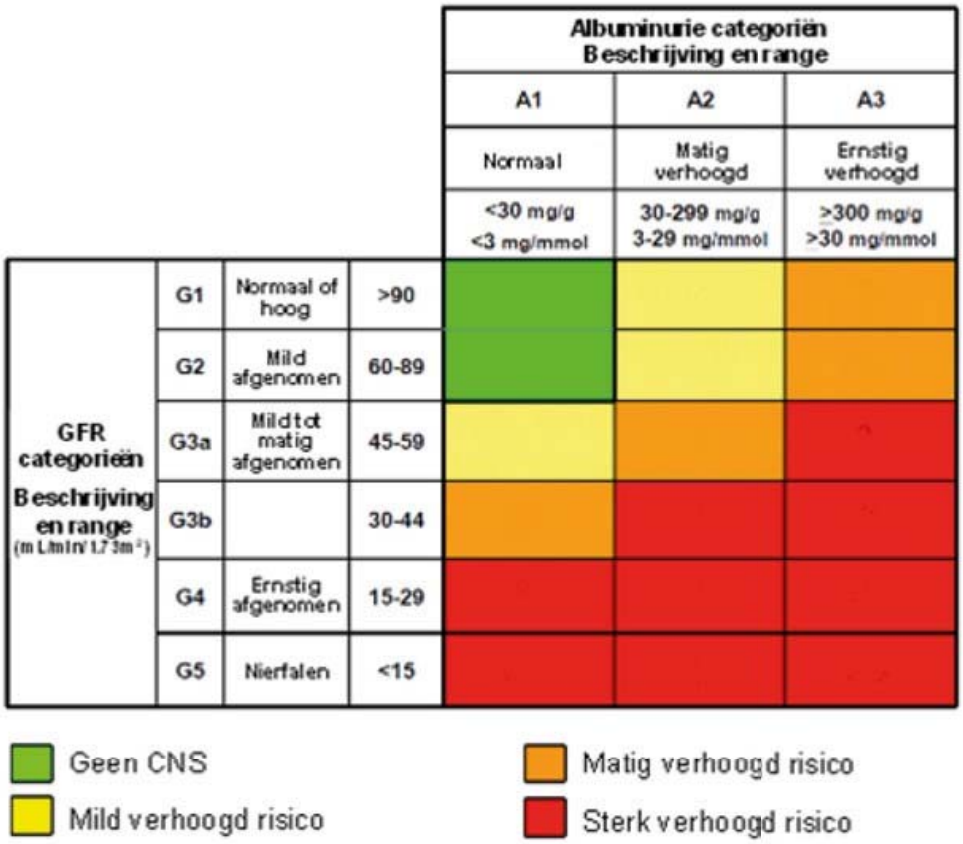
Dit proefschrift bestaat uit 2 delen. Deel 1 heeft als doel nieuwe biomarkers te onderzoeken die kunnen worden gebruikt om CKD progressie te voorspellen. Deel 2 heeft als doel te onderzoeken hoe de nierfunctie het beste kan worden gemonitord over de tijd, zowel wat betreft de keuze van biomarker om de nierfunctie te schatten, als pre-analytische behandeling van bloedmonsters. In dit laatste hoofdstuk worden de belangrijkste bevindingen van ieder hoofdstuk samengevat, en hun implicaties voor toekomstig onderzoek en de klinische praktijk worden besproken.

**Deel 1. Biomarkers voor het voorspellen van CKD progressie**

**Serum bicarbonaat**

Metabole acidose, verzuring van het bloed gekarakteriseerd door lage serum bicarbonaat spiegels, is geassocieerd met een verhoogd risico op eindstadium nierfalen en sterfte in CKD populaties zonder diabetes.[5-9] Het is echter niet bekend of deze associatie ook aanwezig is bij patiënten met diabetes. Er zijn redenen om aan te nemen dat bij patiënten met diabetes deze relatie anders zou kunnen zijn. In **Hoofdstuk 2** hebben we daarom de associaties van serum bicarbonaat met nier- en cardiovasculaire eindpunten en sterfte bestudeerd in een cohort van patiënten met type 2 diabetes en diabetische nierziekte. We vonden dat patiënten met lage

bicarbonaat spiegels inderdaad een verhoogd risico hebben op het ontwikkelen van eindstadium nierfalen en sterfte. Deze associaties waren echter volledig afhankelijk van en verklaard door de nierfunctie aan het begin van de studie.




**Figuur 1** Indeling van patiënten aan de hand van nierfunctie (nierfunctie) en albumine categorie, hetgeen leidt tot een globale stadiering wat betreft risico op het optreden van nierfalen, hart- en vaatziekten en sterfte. CNS: chronische nierschade

Deze bevindingen spreken de bevindingen van eerdere studies tegen die wel een onafhankelijke associatie van serum bicarbonaat met eindstadium nierfalen en sterfte vonden.[5-9] Het belangrijkste verschil tussen die studies en onze studie was dat alle

patiënten in onze studies type 2 diabetes hadden terwijl de andere studies voornamelijk patiënten zonder diabetes hebben geïncludeerd. Sterker nog, toen in meer detail werd gekeken naar de bevindingen van de andere studies, vonden we inderdaad dat na stratificatie voor diabetes status de andere studies ook lieten zien dat lage serum bicarbonaat spiegels geen onafhankelijke associatie hebben met eindstadium nierfalen in deze subgroepen.[6,8,9] Het ontbreken van een nierfunctie-onafhankelijke associatie tussen laag serum bicarbonaat en eindstadium nierfalen, sterfte en cardiovasculaire eindpunten in onze studie, suggereert dat correctie van metabole acidose bij patiënten met diabetes en CKD de uitkomsten voor hen niet verbetert, of gestart zou moeten worden bij een andere drempel dan de 22 mEq/L die wordt geadviseerd door de KDIGO richtlijn.[1] Toekomstig onderzoek zou daarom moeten onderzoeken of en wanneer bicarbonaat suppletie gestart zou moeten worden bij patiënten met CKD en diabetes. Op dit moment worden er 4 gerandomiseerde, gecontroleerde studies uitgevoerd om te onderzoeken wat de voordelen en risico's van bicarbonaat suppletie zijn bij patiënten met CKD, en twee studies richten zich specifiek op patiënten met diabetes.[10-13] Hopelijk zullen de resultaten van die studies leiden tot het ontwikkelen van evidence-based richtlijnen voor de correctie van metabole acidose in patiënten met diabetes en CKD.

**Advanced glycation end products en huid autofluorescentie**

Advanced glycation endproducts (AGEs) zijn irreversibel versuikerde eiwitten, en stapeling van AGEs veroorzaakt ontsteking en weefselschade.[14-24] AGEs die opgeslagen liggen in de huid weerkaatsen ultraviolet licht van bepaalde golflengtes, en die zogenoemde huid autofluorescentie kan worden gemeten met een AGE-reader en gebruikt om te berekenen hoeveel AGEs er aanwezig zijn in de huid. Huid autofluorescentie is daarmee een gevalideerde proxy voor stapeling van AGEs in het lichaam. Er is al aangetoond dat verhoogde huid autofluorescentie geassocieerd is met de aanwezigheid van CKD en diabetes,[22,25] en met progressie van CKD in patiënten met diverse stadia van CKD.[26] Het is nog niet bekend of huid autofluorescentie ook geassocieerd is met CKD progressie in patiënten met diabetes mellitus en intacte nierfunctie. In **Hoofdstuk 2** hebben we daarom de associaties van huid autofluorescentie met diabetes en nierfunctieachteruitgang onderzocht in patiënten met perifeer vaatlijden en intacte nierfunctie. We vonden geen associatie tussen huid autofluorescentie en nierfunctie achteruitgang, en deze associatie was ook niet verschillend voor mensen met en zonder diabetes. Deze resultaten spreken de resultaten van de enige eerder uitgevoerde studie die de associatie tussen huid autofluorescentie en nierfunctieachteruitgang onderzocht tegen.[26] Die andere studie is uitgevoerd in Japans CKD cohort, waarin gevonden werd dat huid autofluorescentie geassocieerd is met nierfunctieachteruitgang in patiënten met stadium 1-5 CKD. We hebben twee mogelijke verklaringen voor deze tegenstrijdige resultaten. Ten eerste, de Japanse studie gaf geen informatie over cardiovasculaire

comorbiditeit aan het begin van de studie, en het is bekend dat patiënten met cardiovasculair lijden (inclusief perifeer vaatlijden) hogere huid autofluorescentie waardes hebben. De gemiddelde huid autofluorescentie waarde was in onze studie inderdaad beduidend hoger dan in het Japanse cohort, wat suggereert dat ons cohort een hogere prevalentie van cardiovasculaire comorbiditeit had. Het is daarom mogelijk dat huid autofluorescentie nierfunctieachteruitgang niet voorspelt bij patiënten die al hoge huid autofluorescentie waardes hebben door cardiovasculair lijden. Daarnaast worden AGEs uitgescheiden door de nier, en daarmee zijn AGE waardes afhankelijk van de nierfunctie.[18] Het is mogelijk dat AGE accumulatie ten gevolge van een slechte nierfunctie pas ontstaat als de nierfunctie is gedaald tot onder een bepaalde waarde. Aangezien onze patiënten een intacte nierfunctie hadden aan het begin van de studie, zou dit een reden kunnen zijn voor het ontbreken van een associatie tussen huid autofluorescentie en nierfunctieachteruitgang. De conclusie die uit die uit dit hoofdstuk wordt getrokken is dat huid autofluorescentie geen goede voorspeller van nierfunctieachteruitgang is in patiënten met intacte nierfunctie en perifeer vaatlijden.

**Biomarker panels om progressie van nierziekte te voorspellen**

**Hoofdstukken 2 en 3** zijn voorbeelden van traditioneel biomarker onderzoek in CKD. De associaties van één marker met klinische eindpunten zoals eindstadium nierfalen worden onderzocht om te bepalen of de marker-uitkomst associatie onafhankelijk is van andere risicofactoren voor CKD progressie. Albuminurie en nierfunctie zijn op dit moment de belangrijkste markers voor het voorspellen van CKD progressie. Veel andere markers zijn onderzocht in studies met vergelijkbare methodes als hoofdstuk 2 en 3, maar tot nu toe heeft geen van die markers albuminurie en nierfunctie overtroffen met betrekking tot het voorspellen van nier gerelateerde eindpunten. CKD is een ziekte die bestaat uit veel factoren, en waarbij progressie wordt bepaald door diverse pathofysiologische routes. Het zou daarom nodig kunnen zijn om meerdere markers te gebruiken om zo de informatie over al deze routes te kunnen combineren om een optimale formule voor risicovoorspelling te verkrijgen. In **Hoofdstuk 4** hebben we daarom een review uitgevoerd van de literatuur over biomarker panels voor het voorspellen van CKD progressie, specifiek voor patiënten met type 2 diabetes. We hebben de methodologie van negen studies geanalyseerd die biomarker panels voor het voorspellen van progressie van diabetische nierziekte hebben onderzocht,[27-35] gebaseerd op de criteria zoals gepresenteerd in Box 1. We vonden dat alle studies zich in de vroege stadia van het biomarker ontwikkelingsproces bevonden en dat geen van hen de stappen onderzochten die noodzakelijk zijn voor het implementeren van een biomarker panel in de klinische praktijk: het bestuderen van het biomarker panel in diverse patiënten cohorten (klinisch nut, vroege of late fase van de ziekte), en het bestuderen van het effect dat een biomarker panel kan hebben op behandeling voor het verbeteren van klinische uitkomsten. Derhalve is de conclusie

van dit hoofdstuk dat biomarker panels veelbelovende resultaten boeken voor verbeterde voorspelling van CKD progressie, maar dat de nodige studies om die biomarker panels te controleren op hun juistheid (validatie) voor gebruik in de klinische praktijk ontbreken. Om deze kloof in onze kennis te dichten presenteerden we belangrijke punten om studie ontwerp en methodologie voor het ontwikkelen van biomarker panels bij chronische nierziekte te verbeteren.

**Box 1 Essentiële punten voor het beoordelen of uitvoeren van biomarker studies**

**Ontwikkelingsfase**
- Aantonen dat een marker nuttig kan zijn voor de praktijk
- Associatie met harde eindpunten (zoals eindstadium nierfalen)
- Beoordelen van toegevoegde waarde
- Klinisch nut
- Klinische toepasbaarheid

**Populatie**
- Vroege of late fase van de ziekte

**Eindpunten**
- Surrogaat eindpunten
- Harde eindpunten

**Het meten van biomarkers**
- Selectie van de matrix (bloed, urine)
- Behandeling, invriezen en opslag van monsters voorafgaand aan analyse
- Assay karakteristieken
- Afkapwaarden van de biomarker

**Statistische analyse**
- Grootte van de studie en aantal events
- Corrigeren voor covariabelen (etiologisch of voorspellend)
- Discriminatie (AUC, NRI, IDI)
- Calibratie van het model (observed en expected event rates)

**Deel 2. Biomarkers voor het monitoren van nierfunctie daling Kreatinine assays**

In epidemiologische studies en klinische onderzoeken wordt nierfunctie meestal geschat met behulp van de hoeveelheid kreatinine in het bloed, leeftijd en geslacht. Kreatinine is een afbraakproduct van skeletspieren en wordt daardoor continue geproduceerd. Het is een eiwit dat klein genoeg is om uitgescheiden kan worden door de nieren, en daarmee kan de hoeveel het kreatinine in het bloed worden gebruikt als maat voor de nierfunctie. Door regelmatig het kreatinine te meten kan de snelheid van nierfunctieachteruitgang (de nierfunctie slope) in kaart worden gebracht. Kreatinine wordt meestal gemeten tijdens ieder patiëntenbezoek en de nierfunctie wordt dan geschat met die kreatinine waarde. Een andere optie is om alle monsters die verzameld zijn tijdens het onderzoek op te slaan en dan aan het einde een alle monsters per individu tegelijk te onderzoeken onder dezelfde analytische omstandigheden (single run analyse). Hierdoor wordt het effect van dag tot dag variabiliteit geëlimineerd. Aan de andere kant kan het gebruik van langdurig opgeslagen monsters ook variabiliteit veroorzaken. Het is op dit moment nog niet duidelijk of single run analyse van de verzamelde monsters per patiënt betrouwbaar de rnierfunctieslopes genereert dan routinemetingen uit verse samples. Het is ook nog niet bekend welk kreatinine assay de meest betrouwbare nierfunctie slopes oplevert. Er zijn twee assays beschikbaar om kreatinine te meten: de Jaffe en de enzymatische methode. Hoewel Jaffe assays goedkoper zijn, worden enzymatische assays beschouwd als meer betrouwbaar doordat er minder chemische interferentie door andere stoffen is.[36,37] In **Hoofdstuk 5**, gebruik makend van data van de SUN-MACRO studie, onderzochten we daarom welke methode de meest betrouwbare nierfunctie slope op basis van kreatinine zou opleveren: het gebruik van een Jaffe of een enzymatisch assay, en routine of single-run meting. De originele studie maakte gebruik van routine Jaffe metingen, en in deze studie werden alle monsters opnieuw gemeten middels een single run meting met zowel een Jaffe als enzymatische methode. Zo ontstonden voor iedere patiënt 3 nierfunctie slopes die we met elkaar hebben vergeleken. De meest betrouwbare nierfunctie slope, en dus de meest betrouwbare methode, werd gedefinieerd als de slope met de laagste intra- en inter-individuele variabiliteit en de hoogste biologische geloofwaardigheid. Intra- individuele variabiliteit is gedefinieerd als de nierfunctie variabiliteit over de tijd binnen een patiënt, inter-individuele variabiliteit is gedefinieerd als nierfunctie variabiliteit over de tijd op groepsniveau. Biologische geloofwaardigheid van nierfunctie slopes is gedefinieerd als de waarschijnlijkheid dat een nierfunctie slope het gevolg is van daadwerkelijke verandering in nierfunctie, en niet van andere factoren (zoals bijvoorbeeld laboratoriumvariatie of opslag van bloedmonsters voorafgaand aan de meting). Aangezien patiënten met een snelle nierfunctieachteruitgang een verhoogd risico hebben op het ontwikkelen van eindstadium nierfalen, is het biologisch geloofwaardig dat nierfunctie slopes geassocieerd zijn met gevestigde risicofactoren

voor CKD progressie, zoals albuminurie, en ziekten die geassocieerd zijn met eindstadium nierfalen, zoals hart- en vaatziekten en sterfte. We vonden dat de originele, op Jaffe gebaseerde nierfunctie slopes, de single run methodes overtroffen wat betreft de intra- en inter-individuele variabiliteit en biologische geloofwaardigheid. We vonden geen verschil in intra- en inter-individuele variabiliteit of biologische geloofwaardigheid tussen de nierfunctie slopes verkregen met een single run methode met ofwel een Jaffe dan wel een enzymatisch assay. Dit zijn verrassende resultaten aangezien we verwachtten dat kreatinine op basis van single run met een enzymatisch assay de meest betrouwbare nierfunctie slopes zou opleveren. Van enzymatische assays is al aangetoond dat ze superieur zijn ten opzichte van Jaffe assays, en single run analyse voorkomt variabiliteit ten gevolge van dag-tot-dag variabiliteit van de assays. We hebben twee mogelijke verklaringen voor deze onverwachte resultaten. Ten eerste is het mogelijk dat het langdurig invriezen van de monsters gedurende ongeveer 10 jaar, samen met vries-dooi cycli de kwaliteit van de monsters negatief heeft beïnvloed. Ten tweede wordt de Jaffe methode inferieur beschouwd ten opzichte van enzymatische methodes om kreatinine te meten omdat er sprake is van chemische interferentie met diverse stoffen, zoals albumine en glucose.[36] Aangezien deze stoffen min of meer constante spiegels neigen te hebben binnen patiënten, zou het best zo kunnen zijn dat dit geen invloed heeft op nierfunctie slopes die zijn gecalculeerd met een middels Jaffe methode verkregen kreatinine meting. Uit dit hoofdstuk concluderen we dat het single run meten van kreatinine het gebruik van verse monsters niet overtreft voor het monitoren.

**Kreatinine versus cystatine C in een op de algemene bevolking gebaseerde cohort studie**

Kreatinine, de meest gebruikte biomarker voor het schatten van nierfunctie, is niet accuraat bij patiënten met relatief extreem grote of kleine spiermassa in verhouding tot hun leeftijd en geslacht.[36] Daarom is cystatine C geïntroduceerd als alternatieve nierfunctiemarker. In tegenstelling tot kreatinine wordt cystatine C niet allen door spiercellen, maar door alle cellen in het menselijk lichaam gemaakt. Cystatine C is daardoor minder afhankelijk van spiermassa. Het CKD-EPI consortium heeft formules ontwikkeld waarmee de nierfunctie kan worden geschat met behulp van kreatinine, cystatine C en een combinatie van kreatinine en cystatine C.[38,39] Studies om nieuwe nierfunctiemarkers te valideren worden traditioneel alleen uitgevoerd met eenmalige schattingen van nierfunctie, maar de nierfunctiemarker die een eenmalige nierfunctie meting het beste schat is mogelijk niet de beste marker voor het monitoren van nierfunctieverandering. Daarom hebben we in **Hoofdstuk 6** onderzocht of kreatinine of cystatine C de beste nierfunctiemarker is voor monitoren van nierfunctie verandering in een groot Nederlands, op de algemene bevolking gebaseerde cohort studie. Gebruik makend van dezelfde statistische methoden als in hoofdstuk 5 vonden we dat de intra- en inter-individuele variabiliteit het laagst was voor op

kreatinine gebaseerde slopes. Daarentegen hadden op cystatine C gebaseerde slopes een significant sterkere associatie met risicofactoren voor CKD progressie dan op kreatinine gebaseerde slopes. We hebben het onderzoek naar de biologische geloofwaardigheid uitgebreid met Cox regressieanalyses om de marker die nierfunctie slopes opleverde met de sterkste associatie met het optreden van cardiovasculair lijden en sterfte te achterhalen. We vonden dat de associaties met sterfte gelijkwaardig waren voor alle markers, maar dat alleen op kreatinine gebaseerde slopes geassocieerd waren met cardiovasculair lijden. Twee andere studies hebben ook de associatie van nierfunctie slopes op basis kreatinine en cystatine C met cardiovasculaire events en sterfte onderzocht.[40,41] Zij vonden ook dat de associaties van nierfunctie slopes met sterfte (door alle oorzaken) voor elke marker gelijkwaardig waren, maar dat de op kreatinine gebaseerde slopes een sterkere associatie hadden met cardiovasculair lijden. We concluderen daarom dat voor het monitoren van nierfunctie achteruitgang in de algemene populatie cystatine C niet consequent beter is dan kreatinine, alleen noch in combinatie met kreatinine.

**Kreatinine, cystatine C, Beta-2-Microglobuline, en Beta-Trace protein in een cohort met diabetische nierziekte**

Naast kreatinine en cystatine C zijn er recentelijk twee nieuwe nierfunctiemarkers geïntroduceerd: Beta-2-Microglobulin (B2M) en Beta-Trace protein (BTP). Beide markers worden continu geproduceerd, volledig uitgescheiden door de nier en niet opnieuw opgenomen in bloedbaan na uitscheiding, wat het veelbelovende kandidaten als nierfunctiemarker maakt. Het CKD-EPI consortium heeft drie nieuwe formules ontwikkeld om nierfunctie te schatten met B2M, BTP en B2M plus BTP.42 Daarom hebben we in **Hoofdstuk 7** herhaalde metingen van 4 markers voor het schatten van nierfunctie geanalyseerd: kreatinine, cystatine C, B2M en BTP. Net als in hoofdstuk 5 gebruikten we data van de SUN-MACRO studie. Ons doel was om de beste marker of combinatie van markers te vinden om nierfunctieachteruitgang te monitoren, wederom met dezelfde statistische methoden als in hoofdstuk 5. We vonden dat de intra- en inter-individuele variabiliteit het laagst was voor nierfunctie slopes die geschat zijn met gebruik van BTP, wat suggereert dat nierfunctie slopes preciezer kunnen worden geschat met op BTP. Op cystatine C gebaseerde slopes hadden de sterkste associatie met risicofactoren voor CKD progressie en dus de hoogste biologische geloofwaardigheid. Het verschil tussen in biologische geloofwaardigheid tussen op cystatine C gebaseerde en op kreatinine gebaseerde nierfunctie schattingen was echter niet significant. Daarom concluderen we dat geen van de nieuwe nierfunctiemarkers, alleen of gecombineerd, consequent beter presteerde dan kreatinine voor het monitoren van nierfunctieachteruitgang. Als de resultaten van hoofdstuk 6 en 7 worden gecombineerd kunnen we concluderen dat er nog geen reden is om kreatinine te vervangen door (combinaties van) nieuwe nierfunctiemarkers.

**Gemeten nierfunctie versus nierfunctie en hun associatie met klinische eindpunten**

De studies die beschreven worden in hoofdstukken 5, 6 en 7 hebben allemaal de beperking dat de nierfunctie niet nauwkeurig gemeten maar geschat was met behulp van de bloed kreatinine waarde. Een nauwkeurige meting van de nierfunctie was niet beschikbaar door de kosten die verbonden zijn aan het verkrijgen van herhaalde nierfunctie metingen in een grote studie. De ware nierfunctie, de gouden standaard, is de klaring van inuline door de nieren gedurende 24 uur. Het is echter onmogelijk om zo'n dure en onhandige procedure in de klinische praktijk in te voeren. Als alternatief kan de nierfunctie ook worden geschat middels 3 methodes: nierfunctie berekenen met de plasma of urineklaring van een stof die niet door het lichaam zelf geproduceerd wordt (een exogene marker), zoals iohexol of iothalamaat (hierna beschreven als gemeten nierfunctie), het meten van de 24-uurs urineklaring van een stof die door het lichaam zelf geproduceerd wordt zoals kreatinine of ureum (een endogene marker) en het schatten van de nierfunctie met een formule die serum kreatinine, leeftijd, geslacht en ras combineert, zoals de CKD-EPI formule (hierna beschreven als geschatte nierfunctie).[43] Hoewel wordt aangenomen dat het meten van de nierfunctie op basis van de klaring van een exogene marker de gouden standard is, is het nog onduidelijk welke van deze drie methodes de nierfunctie oplevert met de sterkste associatie met harde eindpunten zoals eindstadium nierfalen en sterfte. In **Hoofdstuk 8** hebben we daarom de huidige literatuur over de drie nierfunctie schattingsmethodes geanalyseerd, en specifiek gemeten nierfunctie en geschatte nierfunctie vergeleken met betrekking tot het voorspellen van klinische eindpunten. We vonden dat zes studies de associatie van gemeten nierfunctie en geschatte nierfunctie met sterfte hebben onderzocht.[40,44-48] De studies hadden uiteenlopende resultaten. Sommige studies vonden dat geschatte nierfunctie, en anderen juist dat gemeten nierfunctie sterkere associaties had met eindstadium nierfalen en sterfte, terwijl anderen geen verschil tussen geschatte en gemeten nierfunctie vonden. Over het algemeen laten deze data zien dat gemeten nierfunctie de geschatte nierfunctie niet consequent overtreft met betrekking tot de associatie met eindstadium nierfalen en sterfte. Een mogelijke verklaring voor deze tegenstrijdigheid is een gebrek aan standaardisatie van de procedure om een gemeten nierfunctie te verkrijgen. Formules om nierfunctie te schatten worden beoordeeld door ze te vergelijken met gemeten nierfunctie. Maar aangezien gemeten nierfunctie verkregen kan worden met diverse exogene nierfunctiemarkers, en omdat er geen standaardisatie is van de protocollen en assays die worden gebruikt om gemeten nierfunctie te verkrijgen, is er altijd bias en onnauwkeurigheid binnen de diverse gemeten nierfunctie markers. Deze bias is ook aanwezig als gemeten nierfunctie wordt vergeleken met geschatte nierfunctie, en dus kan een verschil tussen geschatte en gemeten nierfunctie (als beiden bepaald worden in dezelfde

patiënten) niet alleen maar het gevolg zijn van onnauwkeurigheid van de geschatte nierfunctie. Aan de andere kant is geschatte nierfunctie verkregen met kreatinine over de hele wereld gestandaardiseerd, zowel wat betreft het assay als de formule om nierfunctie te schatten.[1,49] Als deze resultaten en overwegingen worden gecombineerd met het feit dat geschatte nierfunctie ook nog eens verkregen kan worden voor een fractie van de kosten van een gemeten nierfunctie, concluderen we dat geschatte nierfunctie mogelijk helemaal niet inferieur is aan gemeten nierfunctie.

**Toekomstperspectieven**

**Box 2 Implicaties van dit proefschrift voor de praktijk:**

- Serum bicarbonaat spiegels kunnen het verhoogde risico op eindstadium nierfalen en sterfte bij patiënten met type 2 diabetes niet verklaren.
- Huid autofluorescentie kan niet gebruikt worden voor het voorspellen van nierfunctieachter- uitgang in patiënten met perifeer vaatlijden.
- Biomarker panels kunnen nog niet worden geïmplementeerd in de nefrologiepraktijk door een gebrek aan validatiestudies.
- Ieder kreatinine assay kan worden gebruikt voor het monitoren van nierfunctieachteruitgang zo lang het maar gekalibreerd is volgens internationale standaarden.
- Er is nog geen reden om kreatinine te vervangen door nieuwe markers voor het monitoren van nierfunctieachteruitgang.
- Procedures om de gemeten nierfunctie te verkrijgen moeten worden gestandaardiseerd zodat studies ter validatie van alternatieve nierfunctiemarkers kunnen worden verbeterd.

**Van individuele markers naar biomarkerpanels voor het voorspellen van CKD progressie**

De implicaties voor de praktijk van dit proefschrift worden samengevat in Box 2. Er kunnen twee hoofdconclusies getrokken worden uit deel 1 van dit proefschrift. Ten eerste, albuminurie en nierfunctie worden op dit moment gebruikt om CKD de diagnosticeren en stadiëren, en beiden zijn sterke voorspellers van het ontwikkelen van eindstadium nierfalen en sterfte. Een nieuwe biomarker moet toegevoegde voorspellende waarde hebben bovenop deze bekende markers om klinisch zinvol te zijn. Gezien de sterke voorspellende waarde van albumine en nierfunctie zal het lastig worden om afzonderlijke biomarkers te vinden die een significante en relevante

verbetering bieden ten opzichte van bestaande markers. Ten tweede, biomarkerpanels hebben wel de potentie om voorspelling van CKD progressie te verbeteren ten opzichte van albuminurie en nierfunctie, maar de studies die tot nu toe zijn uitgevoerd om zulke biomarkerpanels te ontwikkelen voor de klinische praktijk zijn van onvoldoende kwaliteit. In het bijzonder worden er zelden studies uitgevoerd die een biomarkerpanel onderzoeken in diverse patiënten cohorten, of onderzoeken wat het effect van een biomarkerpanel is op de behandeling om zo de klinische uitkomsten mogelijk te verbeteren.
Deze studies zijn van essentieel belang voor het implementeren van een nieuw biomarkerpanel in de klinische praktijk. Als deze studies niet worden uitgevoerd zullen we nooit weten of behandeling geleid door een biomarkerpanel daadwerkelijk de klinische uitkomsten zal beïnvloeden.
Op dit moment is er nog geen consensus over de criteria die gebruikt moeten worden om de waarde van biomarkers binnen de nefrologie te bepalen. Daarom is er een richtlijn nodig voor het valideren van biomarkers en biomarkerpanels. Bestaande kaders die worden gebruikt binnen andere takken van de geneeskunde kunnen hiervoor worden gebruikt. Het kader voor het evalueren van biomarkers binnen de cardiologie, voorgesteld door Hlatky et al., kan bijvoorbeeld worden gebruikt voor biomarkerpanel studies binnen de nefrologie.[50] Het gebruik van zo'n richtlijn of kader kan helpen om de focus van onderzoekers te verleggen van ontdekking van nieuwe biomarkers richting validatie van bestaande biomarkerpanels, bepalen van hun klinische toepasbaarheid, en uiteindelijk implementatie in de klinische praktijk.
Biomarkerpanels kunnen niet alleen gebruikt worden om de predictie van CKD progressie te verbeteren, maar ook om de behandelrespons te evalueren, wat ze ook interessant maakt voor het verbeteren van ontwerpen van toekomstige studies. Als de kans op een gunstige behandelrespons kan worden voorspeld met een biomarkerpanel, zou zo'n panel gebruikt kunnen worden om de optimale studiepopulatie te selecteren: voorspellen van ongunstige reacties om de mate van uitval te beperken, en voorspellen van gunstige reacties om de optimale populatie te selecteren voor een behandeling in de klinische praktijk. Twee voorbeelden van klinische trials die biomarker panels om een doelpopulatie te selecteren voor (onderzoeks-) medicatie zijn de PRIORITY (NCT 02040441) en SONAR studie (NCT 01858532). PRIORITY heeft als doel om het effect van spironolacton versus placebo te bepalen wat betreft het vertragen van het optreden van microalbuminurie (de aanwezigheid van kleine hoeveelheden albumine in de urine) bij patiënten met type 2 diabetes zonder albuminurie. De studie selecteert patiënten gebaseerd op een urine proteomics score. Proteomics is het grootschalig bestuderen van alle eiwitten die aanwezig kunnen zijn in de urine. De eiwitsamenstelling van urine wordt momenteel onderzocht om te zien of dit kan worden gebruikt om het risico op nierziekten te voorspellen. Patiënten met een positieve proteomics score worden geselecteerd aangezien zij een grotere kans hebben op het ontwikkelen van

microalbuminurie en zij zullen willekeurig worden ingedeeld om spironolacton (een bloeddrukverlager die tevens de uitscheiding van albumine in de urine vermindert) of placebo te ontvangen. Patiënten met een negatieve proteomics score worden gevraagd om deel te nemen aan een prospectieve cohortstudie.[51] Het andere voorbeeld is de SONAR studie. Hoewel SONAR niet het effect van een specifieke biomarker score onderzoekt, gebruikt het wel diverse biomarkers om vast te stellen wie voordeel zou kunnen hebben van behandeling met atrasentan, een nieuw medicijn dat is ontwikkeld om progressie van nierziekte te vertragen. SONAR gebruikt een open-label verrijkingsfase, waarin iedere patiënt atrasentan ontvangt. Patiënten kunnen alleen deelnemen aan de daaropvolgende dubbelblinde behandelfase als ze een gunstige respons hebben van een gecombineerd veiligheids- en effectiviteitspanel, waaronder albuminurie, lichaamsgewicht, kreatinine en brain natriuretic peptide (een maat voor de vochtbelasting van het hart en het lichaam). Tezamen zullen deze studies hopelijk aantonen dat biomarkerpanels inderdaad patiënten kunnen identificeren die de grootste kans hebben op een gunstige respons op onderzoeksmedicatie. Bovendien zou dit kunnen leiden tot een nieuwe standaard voor studie ontwerp, waarbij biomarkerpanels bestaande uit zowel veiligheids- als effectiviteitsmarkers zullen worden gebruikt om de doelpopulatie voor nieuwe medicijnen voor de behandeling van CKD te bepalen. Dit zou niet alleen kunnen leiden tot studies met minder uitval of lagere incidentie van nadelige bijwerkingen, het zou ook kunnen helpen bij het registeren van nieuwe medicatie voor specifieke indicaties. Daarmee helpt het artsen om het juiste medicijn voor te schrijven aan de juiste patiënt. In een era waarin personalized medicine in opkomst is, zijn dit belangrijke ontwikkelingen.

**Het monitoren van nierfunctie over de tijd**

Deel 2 van dit proefschrift concentreerde zich op welke marker en welk assay het beste is voor het monitoren van nierfunctie over de tijd. Wat betreft kreatinine assays concludeerden we dat voor het monitoren van nierfunctie achteruitgang het in een single run meten van kreatinine uit plasma monsters die bevroren bewaard zijn niet superieur is aan het gebruik van verse monsters, onafhankelijk van het gebruikte kreatinine assay. Deze resultaten suggereren dat het gunstige effect van minder variabiliteit door assay-geïnduceerde drift en dag-tot-dag variabiliteit op de kreatinine metingen niet opweegt tegen de ongunstige effecten van langdurige opslag van serum monsters en vries-dooi cycli. Onze resultaten suggereren dat het niet noodzakelijk is om de huidige gewoonte van tijdens klinische studies kreatinine te meten uit verse monsters te veranderen naar een single run meting aan het einde van de studie. Daarentegen kan onze bevinding dat nierfunctie slopes niet beïnvloed worden door het gebruikte kreatinine assay wel toekomstige studies beïnvloeden. De Jaffe methode wordt nog altijd gebruikt omdat het goedkoper is dan enzymatische assays. Met de kennis dat het voor herhaalde nierfunctie metingen niet uitmaakt welk

kreatinine assay gebruikt wordt, betekent deze vinding dat robuust nefrologie onderzoek ook uitgevoerd kan worden in gebieden met beperkte onderzoeksgelden. Hoofdstuk 6 en 7 lieten zien dat geen van de nieuwe markers kreatinine overtroffen voor het monitoren van nierfunctie over de tijd. Bovendien presteerden zelfs combinaties van biomarkers niet beter dan kreatinine. Hierbij moet wel de kanttekening worden geplaatst dat dit alleen geldt voor herhaalde metingen van nierfunctie. Voor enkele metingen van nierfunctie leidt het combineren van kreatinine en cystatine C wel degelijk tot een meer accurate schatting van de gemeten nierfunctie.[42] Het is mogelijk dat net als bij de vergelijking van Jaffe en enzymatische assays voor het meten van kreatinine, de mogelijke (systematische) onnauwkeurigheid voor een puntschatting van nierfunctie geen invloed heeft op de nierfunctie slopes.

Vier stappen moeten worden genomen om een definitieve keuze van een marker voor nierfunctie monitoring in de toekomst te kunnen maken. Als eerste moeten de geschatte nierfunctie slopes van elke marker worden vergeleken met de bijbehorende gemeten nierfunctie slopes. Ten tweede moeten toekomstige studies onderzoeken welke marker of combinatie van markers leidt tot nierfunctie slopes met de sterkste associatie met harde eindpunten zoals eindstadium nierfalen en sterfte. Ten derde, behandeleffecten op nierfunctie slopes gebaseerd op de diverse nierfunctiemarkers moeten worden beoordeeld en vergeleken. Ten vierde, in aanvulling op onze eerdere oproep voor de ontwikkeling van biomarkerpanels, is het noodzakelijk om formules te ontwikkelen om de nierfunctie te schatten waarbij B2M en/of BTP wordt toegevoegd aan kreatinine en cystatine C, en dat deze uitgebreid worden getest in diverse populaties. De marker of combinatie van markers die een nierfunctie slope opleveren die het dichtst in de buurt komt van de ware nierfunctie en die de minste variabiliteit heeft door invloeden buiten de nier om (bijvoorbeeld assay variabiliteit of biologische variabiliteit) moet worden gekozen. Onze resultaten uit Hoofdstuk 7 suggereren dat het gebruik van een multi-marker formule de schatting van nierfunctie daling niet lijkt te verbeteren. Hierbij moet echter wel worden opgemerkt dat onze studie een relatief korte follow-up duur had en dat harde eindpunten zoals eindstadium nierfalen niet beschikbaar waren. Daarom is het nog altijd nodig om deze markers te onderzoeken in diverse populaties en cohorten met lange follow-up duur om een definitief antwoord te kunnen geven op de vraag welke marker het beste is voor het monitoren van nierfunctie. In de praktijk zou de keuze voor een marker kunnen afhangen van specifieke patiënteigenschappen. Kreatinine is bijvoorbeeld niet geschikt als nierfunctiemarker in studies met een behandeling die een direct effect heeft op de kreatinine productie of excretie, zoals een dieet met een laag eiwitgehalte. In die gevallen zou cystatine C of een van de andere markers een betere keuze kunnen zijn. Het gebruik van een combinatie van markers zou ook kunnen helpen om de beperking van individuele markers te ondervangen.

Inuline wordt beschouwd als de gouden standaard voor het meten van de nierfunctie, waartegen iedere marker en formule voor het schatten van de nierfunctie wordt gevalideerd. We hebben echter in Hoofdstuk 8 laten zien dat er aanzienlijke analytische variatie is van gemeten nierfunctie, mogelijk veroorzaakt door een gebrek aan standaardisatie. Alle endogene nierfunctiemarkers die worden gebruikt om de nierfunctie te schatten worden gevalideerd ten opzichte van de gemeten nierfunctie. Het is belangrijk om daarbij op te merken dat zolang de gemeten nierfunctie niet wordt verkregen middels een betrouwbare en gestandaardiseerde methode, er altijd bias en onnauwkeurigheid zal ontstaan voor de geschatte nierfunctie die niet alleen toegeschreven kan worden aan de endogene nierfunctiemarker. Daarom moeten de gemeten nierfunctie worden gestandaardiseerd op drie niveaus: standaardisatie van de gebruikte marker, het meten van de markers in het plasma, en standaardisatie van de procedure omtrent het meten van de nierfunctie. Net als bij de keuze van een nierfunctiemarker om de nierfunctie te schatten, zou het kunnen dat de meest geschikte procedure voor het meten van de nierfunctie afhangt van de context en indicatie. Delenaye et al. hebben recent een pragmatische aanpak voorgesteld voor het gebruik van gemeten nierfunctie in onderzoek en de klinische praktijk.[52] Zij stellen voor dat meerdere monsters moeten worden verzameld met diverse intervallen in situaties waarbij gemeten nierfunctie wordt gebruikt als referentiemethode tijdens de ontwikkeling van nieuwe formules om nierfunctie te schatten. Daarentegen is een minder gecompliceerd protocol met een laat verzameld monster of een enkel verzameld monster nodig voor epidemiologische studies of in situaties waarbij nierfunctie een secundair eindpunt is.

**Conclusie**

In deel 1 van dit proefschrift hebben we laten zien dat een aantal enkele biomarkers CKD progressie niet beter voorspellen dan gevestigde risicomarkers voor CKD progressie, zoals nierfunctie en albuminurie. We adviseren om toekomstig onderzoek te richten op combinaties van biomarkers (biomarkerpanels) om zo nauwkeuriger de kans op CKD progressie te kunnen voorspellen. In deel 2 van dit proefschrift hebben we laten zien dat nieuwe nierfunctiemarkers en zelfs nierfunctie gemeten met exogene markers niet consequent nierfunctie gebaseerd op kreatinine overtreffen voor het monitoren van nierfunctie verandering over de tijd. Daarom is er vooralsnog geen reden om kreatinine, dat op dit moment de klinisch meest gebruikte en goedkoopste marker is om nierfunctie verandering te monitoren, te vervangen door andere biomarkers.

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# Longgeneeskunde

Self-management exacerbation action plans in patients with chronic obstructive pulmonary disease and common comorbidities: The COPE-III study

Proefschrift

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Prof. dr. T.T.M. Palstra
volgens besluit van het College voor Promoties.
in het openbaar te verdedigen
op vrijdag 15 september 2017 om 14:45 uur

door

**Anke Lenferink**

geboren op 17 november 1985 te
Tubbergen

Promotor: Prof. dr. J.A.M. van der Palen
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Prof. dr. H.A.M. Kerstjens

**Samenvatting**
Chronic Obstructive Pulmonary Disease (COPD) is een chronische progressieve longaandoening. Deze longziekte wordt gekenmerkt door klachten van kortademigheid, slijmproductie, hoesten en een piepende ademhaling, met exacerbaties – longaanvallen, acute verergering van longklachten - welke bijdragen aan verminderde kwaliteit van leven en meer ziekenhuisopnames, mortaliteit en zorgkosten. COPD wordt beschouwd als een complexe, heterogene en multi-componente ziekte. Veelvoorkomende comorbiditeiten bij COPD, zoals cardiovasculaire ziekten, psychische klachten en diabetes, hebben een belangrijke impact op de ernst van de ziekte, ziekenhuisopnames en overleving. Deze comorbiditeiten delen dezelfde algemene risicofactoren als COPD, zoals veroudering, roken en inactiviteit. Daarnaast kennen COPD en comorbiditeiten een overlap van klachten, bijvoorbeeld kortademigheid of vermoeidheid. Bij COPD patienten met daarnaast de complexiteit van comorbiditeiten zal een 'one size fits all' benadering, die zich enkel richt op COPD klachten, inadequaat zijn. Dit kan namelijk leiden tot een vertraagde of verkeerde (zelf)behandeling. Multi-componente COPD zelfmanagement interventies, die zich richten op gedragsverandering, zijn belangrijk in de management van COPD patienten. Exacerbatie actieplannen zijn een essentieel onderdeel van deze COPD zelfmanagement interventies.

In **Hoofdstuk 2** hebben we 22 studies geëvalueerd in een Cochrane review. In dit review hebben we de effectiviteit van COPD zelfmanagement interventies met een actieplan voor acute COPD exacerbaties vergeleken met reguliere zorg. De resultaten lieten zien dat zelfmanagement interventies met COPD exacerbatie actieplannen zijn geassocieerd met een verbetering van de kwaliteit van leven en een lagere kans op respiratoir-gerelateerde opnames, zonder buitensporige mortaliteit. Voor toekomstige studies adviseren we om alleen actieplannen te gebruiken als deze onderdeel zijn van zelfmanagement interventies, welke gestructureerd en gepersonaliseerd zijn en bestaan vaak uit meerdere componenten. Deze interventies hebben als doel om de patienten te motiveren, te betrekken en te ondersteunen om positieve gedragsverandering te bewerkstelligen en om vaardigheden te ontwikkelen om beter te kunnen omgaan met hun ziekte. Als studie auteurs meer gedetailleerde informatie geven over de aangeboden interventies, dan zal de transparantie over de zelfmanagement interventie componenten, de actieplan componenten en de technieken voor gedragsverandering vergroot kunnen worden. Hierdoor zullen betere aanbevelingen gegeven kunnen worden omtrent effectieve zelfmanagement interventies met actieplannen voor COPD exacerbaties. De veiligheid van zelfmanagement interventies zal kunnen worden verbeterd als in COPD zelfmanagement actieplannen rekening wordt gehouden met comorbiditeiten. Wij hebben deze strategie echter niet kunnen evalueren in ons review.

In **Hoofdstuk 3** beschrijven we het ontwerp van de COPE-III zelfmanagement interventie, waarin zelf-geïnitieerde persoonlijke actieplannen voor COPD en comorbiditeiten (chronisch hartfalen, ischemische hartziekten, angst, depressie, diabetes mellitus) worden gecombineerd met doorlopende casemanager ondersteuning. In samenwerking met multi-disciplinaire ziekte-experts hebben we een dagelijks klachtendagboek voor klachtenmonitoring ontwikkeld en hieraan gelinkte actieplannen voor de zelfbehandeling van de individuele COPD en comorbide aandoening(en).

In **Hoofdstuk 4** geven we informatie over de integratie van informatie van twee voorgaande COPD zelfmanagement interventies (COPE-I en COPE-II) voor de ontwikkeling van onze COPE-III zelfmanagement interventie. Geadviseerd wordt om het COPE-III actieplan te raadplegen zodra er een duidelijke verergering van klachten optreedt, welke afwijken van de individuele klachten in een stabiele gezondheidstoestand. Dit is vergelijkbaar met de benadering in de COPE-II studie. We hebben geprobeerd om, net zoals in de COPE-I en COPE-II studie, de patientveiligheid te waarborgen door makkelijk toegankelijke doorlopende casemanager ondersteuning te bieden.

In **Hoofdstuk 5** presenteren we een validatie van de Partners in Health (PIH) schaal om zelfmanagement gedrag en kennis van Nederlandse COPD patiënten te meten. Er zijn twee subschalen gevonden voor de Nederlandse PIH data: 1) kennis en omgaan met de aandoening; en 2) herkenning en management van klachten, therapietrouw. We adviseren om deze twee subschaalscores te gebruiken om zelfmanagement in Nederlandse COPD patiënten te beschrijven. Op basis van de gevonden discrepanties tussen de originele Australische PIH en de Nederlandse PIH adviseren we daarnaast om enkele wijzigingen en verfijningen van de PIH door te voeren. We denken dat de PIH veelbelovend is in het identificeren van de (te verbeteren) zelfmanagementvaardigheden in COPD patiënten met comorbiditeiten. Er is echter meer onderzoek nodig om te evalueren of het gebruik van twee subschalen optimaal is in andere populaties. Daarnaast is consensus nodig over een definitieve versie van de PIH, die kan worden gevalideerd in verschillende settings en populaties. Tevens zal een evaluatie van de klinische relevantie en een beschrijving van de responsiviteit van de PIH kunnen helpen om patiënten te identificeren die baat zullen hebben van de COPD zelfmanagement interventies.

In **Hoofdstuk 6** beschrijven we de resultaten van onze internationale multi-center gerandomiseerde gecontroleerde studie. Dit is de eerste studie die bevestigt dat patiënten met COPD en belangrijke comorbiditeiten betere uitkomsten hebben als ze een zelfmanagement interventie ontvangen welke rekening houdt met

comorbiditeiten. De exacerbatie actieplannen voor COPD patiënten met comorbiditeiten - aangeboden in een geindividualiseerde zelfmanagement interventie, bestaande uit meerdere facetten - bleken effectief in het verminderen van de duur van een COPD exacerbatie en respiratoir gerelateerde ziekenhuisopnames, zonder buitensporige mortaliteit. Daarnaast was er bij de patiënten in de zelfmanagementgroep ook een verbetering van het vertrouwen in eigen kunnen om ademhalingsproblemen te voorkomen. De zelfmanagementgroep rapporteerde meer cardiovasculair-gerelateerde opnames. Er was echter geen significant verschil in cardiovasculair-gerelateerde opnames zodra er enkele zelfmanagementgroep patiënten werden geëxcludeerd, die tijdens de follow-up hun eerste cardiovasculairgerelateerde event ervoeren. Zij hadden daarom geen actieplan ontvangen voor hun cardiovasculaire problemen. Verder rapporteerde de zelfmanagementgroep lagere scores voor emotioneel functioneren, welke mogelijk een weerspiegeling zijn van meer bewustzijn van klachten door de zelfmanagementtraining. We hebben educatie en training gebruikt om de zelfregulatievaardigheden van patiënten te verbeteren en om te richten op optimaal passend zelfmanagementgedrag. Het aanbieden van exacerbatie actieplannen voor COPD en comorbiditeiten samen met zelfmanagementtraining moet in acht worden genomen als een behandelingsmogelijkheid voor COPD patiënten met daar bovenop de complexiteit van comorbiditeiten. Deze zelfmanagement interventies moeten verder worden aangepast aan de behoeften en mogelijkheden van de individuele patient. Ook moet worden gefocust op casemanager ondersteuning om het vertrouwen van patiënten in hun eigen kunnen en de mentale gezondheidstoestand van patiënten te verbeteren.

In **Hoofdstuk 7** worden de belangrijkste resultaten van de studies in dit proefschrift bediscussieerd en worden de bevindingen in een bredere context van zelfmanagement interventies geplaatst. Er worden methodologische overwegingen gegeven, bijvoorbeeld de selectie van sterk gemotiveerde patiënten in onze studie sample en een gebrek aan procesevaluatie van de interventie door casemanagers.

Samenvattend zijn onze implicaties voor verder onderzoek en de klinische praktijk:
1. zelfbehandeling van comorbiditeiten overwegen in op de patient aangepaste exacerbatie actieplannen voor COPD patiënten met comorbiditeiten, en deze aanbieden met zelfmanagementtraining en doorlopende casemanager ondersteuning;
2. alleen actieplannen gebruiken in zelfmanagement interventies welke gestructureerd, persoonlijk en vaak multi-component zijn, met als doel om de patiënten te motiveren, te betrekken en te ondersteunen om positieve gedragsverandering te bewerkstelligen en om vaardigheden te ontwikkelen om beter te kunnen omgaan met hun ziekte;

3. studie auteurs moeten meer gedetailleerde informatie geven over de aangeboden zelfmanagement interventie;
4. patientkarakteristieken identificeren welke succesvol COPD zelfmanagement kunnen voorspellen; en
5. consensus bereiken over een definitieve versie van de Partners in Health schaal, die kan worden gebruikt in meerdere settings en populaties.

# PubMed publicaties per vakgroep

# Anesthesiologie

**1. Long-term outcomes and cost effectiveness of high-dose dexamethasone for cardiac surgery: a randomised trial.**

Dieleman JM, de Wit GA, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, de Lange F, Boer C, Neslo RE, Moons KG, van Herwerden LA, Tijssen JG, Kalkman CJ, van Dijk D.

Prophylactic intra-operative administration of dexamethasone may improve short-term clinical outcomes in cardiac surgical patients. The purpose of this study was to evaluate long-term clinical outcomes and cost effectiveness of dexamethasone versus placebo. Patients included in the multicentre, randomised, double-blind, placebo-controlled DExamethasone for Cardiac Surgery (DECS) trial were followed up for 12 months after their cardiac surgical procedure. In the DECS trial, patients received a single intra-operative dose of dexamethasone 1 mg.kg-1 (n = 2239) or placebo (n = 2255). The effects on the incidence of major postoperative events were evaluated. Also, overall costs for the 12-month postoperative period, and cost effectiveness, were compared between groups. Of 4494 randomised patients, 4457 patients (99%) were followed up until 12 months after surgery. There was no difference in the incidence of major postoperative events, the relative risk (95%CI) being 0.86 (0.72-1.03); p = 0.1. Treatment with dexamethasone reduced costs per patient by pound921 [euro1084] (95%CI pound-1672 to -137; p = 0.02), mainly through reduction of postoperative respiratory failure and duration of postoperative hospital stay. The probability of dexamethasone being cost effective compared with placebo was 97% at a threshold value of pound17,000 [euro20,000] per quality-adjusted life year. We conclude that intra-operative high-dose dexamethasone did not have an effect on major adverse events at 12 months after cardiac surgery, but was associated with a reduction in costs. Routine dexamethasone administration is expected to be cost effective at commonly accepted threshold levels for cost effectiveness.

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Impact factor: 4.741

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Totale impact factor: 4.741
Gemiddelde impact factor: 4.741

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

Gemiddelde impact factor: 0

# Cardiologie

**1. Clopidogrel or ticagrelor in acute coronary syndrome patients treated with newer-generation drug-eluting stents: CHANGE DAPT**
Zocca P, van der Heijden LC, Kok MM, Lowik MM, Hartmann M, Stoel MG, Louwerenburg JW, de Man FHAF, Linssen GCM, Knottnerus IL, Doggen CJM, van Houwelingen KG, von Birgelen C

**Aims:** Acute coronary syndrome (ACS) guidelines have been changed, favouring more potent antiplatelet drugs. We aimed to evaluate the safety and efficacy of a ticagrelor- instead of a clopidogrel-based primary dual antiplatelet (DAPT) regimen in ACS patients treated with newer-generation drug-eluting stents (DES).
**Methods and Results:** CHANGE DAPT (clinicaltrials.gov: NCT03197298) assessed 2,062 consecutive real-world ACS patients, treated by percutaneous coronary intervention (PCI), the primary composite endpoint being net adverse clinical and cerebral events (NACCE: all-cause death, any myocardial infarction, stroke or major bleeding). In the clopidogrel (CP; December 2012-April 2014) and ticagrelor periods (TP; May 2014-August 2015), 1,009 and 1,053 patients were treated, respectively. TP patients were somewhat older, underwent fewer transfemoral procedures, and received fewer glycoprotein IIb/IIIa inhibitors. In the TP, the one-year NACCE rate was higher (5.1% vs. 7.8%; HR 1.53 [95% CI: 1.08-2.17]; p=0.02). Assessment of non-inferiority (pre-specified margin: 2.7%) was inconclusive (risk difference: 2.64 [95% CI: 0.52-4.77]; pnon-inferiority=0.48). TP patients had more major bleeding (1.2% vs. 2.7%; p=0.02) while there was no benefit in ischaemic endpoints. Propensity score-adjusted multivariate analysis confirmed higher NACCE (adj. HR 1.75 [95% CI: 1.20-2.55]; p=0.003) and major bleeding risks during TP (adj. HR 2.75 [95% CI: 1.34-5.61]; p=0.01).
**Conclusions:** In this observational study, the guideline-recommended ticagrelor-based primary DAPT regimen was associated with an increased event risk in consecutive ACS patients treated with newer-generation DES.

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Impact factor: 5.193

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**2. Functional comparison between BuMA Supreme biodegradable polymer sirolimus-eluting and durable polymer zotarolimus-eluting coronary stents using Quantitative Flow Ratio: PIONEER QFR substudy**
Asano T, Katagiri Y, Collet C, Tenekecioglu E, Miyazaki Y, Sotomi Y, Amoroso G, Aminian A, Brugaletta S, Vrolix M, Hernandez-Antolin R, van de Harst P, Iniguez A,

Janssens L, Smits P, Wykrzykowska JJ, Ribeiro VG, Periera H, da Silva PC, Piek JJ, Reiber JHC, von Birgelen C, Sabate M, Onuma Y, Serruys PW

**Aims:** Quantitative Flow Ratio (QFR) based on 3-dimensional quantitative coronary angiography (3D-QCA) is a novel method to assess the physiological functionality after treatment with stents. The current study aimed to evaluate the difference in physiological functionality 9 months after implantation of a bioresorbable polymer-based sirolimus-eluting stent with an electrografting base layer (BuMA Supreme: B-SES) versus a durable polymer-based zotarolimus-eluting stent (Resolute: R-ZES).
**Methods and Results:** The current post-hoc analysis was performed in the PIONEER randomized trial (1:1 randomization to B-SES [83 patients/95 lesions] and R-ZES [87 patients/101 lesions]). QFR was measured in stented vessels in both arms at pre-procedural, post-procedural and 9-month angiography without pharmacologically induced hyperemia (contrast QFR). At 9 months, both the values of QFR distal to the stent (B-SES: 0.89+/-0.10 vs. R-ZES: 0.89+/-0.11, p=0.97) and the numbers of the vessels with QFR </=0.8 were not significantly different between the two groups (11.0% vs. 12.8%, p=0.72), while the in-stent binary restenosis rate was also comparable (3.7% versus 3.5%, P=1.00). QFR gradient across the device (QFR) at 9 months was also similar between both groups (B-SES: 0.03+/-0.04 vs. R-ZES: 0.03+/-0.07, p=0.95).
**Conclusions:** Quantitative flow assessment 9 months after stenting did not differ between B-SES and R-ZES, despite of a significant difference in in-stent late lumen loss**.**

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Impact factor: 5.193

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**3. Influence of Myocardial Ischemia Extent on Left Ventricular Global Longitudinal Strain in Patients After ST-Segment Elevation Myocardial Infarction**
Dimitriu-Leen AC, Scholte AJ, Katsanos S, Hoogslag GE, van Rosendael AR, van Zwet EW, Bax JJ, Delgado V

Two-dimensional echocardiographic left ventricular (LV) global longitudinal strain (GLS) after ST-segment elevation myocardial infarction (STEMI) is moderately correlated with infarct size and reflects the residual LV systolic function. This correlation may be influenced by the presence of myocardial ischemia. The present study investigated how myocardial ischemia modulates the correlation between LV GLS and infarct size determined with single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in patients with first STEMI treated with

primary coronary intervention. A total of 1,128 patients (age 60 +/- 11 years) who underwent SPECT MPI for the evaluation of infarct size and residual ischemia were evaluated. LV GLS was measured on transthoracic echocardiography. The time interval between echocardiography and SPECT MPI was 1 +/- 1 month. A moderate correlation between echocardiographic LV GLS and infarct size on SPECT MPI was observed (r = 0.58, p <0.001). This correlation was weakened by the presence or extent of ischemia; in the group of patients without ischemia, the correlation between LV GLS and infarct size on SPECT MPI was r = 0.66 (p <0.001), whereas in patients with mild or moderate-to-severe ischemia, the correlations were r = 0.56 and 0.38, respectively (both p <0.001). Moderate-to-severe myocardial ischemia was independently associated with more impaired LV GLS after adjusting for infarct size, age, diabetes mellitus, and hypertension (beta 0.60, 95% confidence interval 013 to 1.06). In conclusion, the presence of myocardial ischemia after STEMI impacts on the correlation between echocardiographic LV GLS and infarct size measured on SPECT MPI. Residual ischemia is independently associated with more impaired LV GLS.

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Impact factor: 3.398

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**4. Acute cardioversion vs a wait-and-see approach for recent-onset symptomatic atrial fibrillation in the emergency department: Rationale and design of the randomized ACWAS trial**

Dudink E, Essers B, Holvoet W, Weijs B, Luermans J, Ramanna H, Liem A, van Opstal J, Dekker L, van Dijk V, Lenderink T, Kamp O, Kulker L, Rienstra M, Kietselaer B, Alings M, Widdershoven J, Meeder J, Prins M, van Gelder I, Crijns H

**Background:** Current standard of care for patients with recent-onset atrial fibrillation (AF) in the emergency department aims at urgent restoration of sinus rhythm, although paroxysmal AF is a condition that resolves spontaneously within 24 hours in more than 70% of the cases. A wait-and-see approach with rate-control medication only and when needed cardioversion within 48 hours of onset of symptoms is hypothesized to be noninferior, safe, and cost-effective as compared with current standard of care and to lead to a higher quality of life.
**Design:** The ACWAS trial (NCT02248753) is an investigator-initiated, randomized, controlled, 2-arm noninferiority trial that compares a wait-and-see approach to the standard of care. Consenting adults with recent-onset symptomatic AF in the emergency department without urgent need for cardioversion are eligible for participation. A total of 437 patients will be randomized to either standard care (pharmacologic or electrical cardioversion) or the wait-and-see approach, consisting of symptom reduction through rate control medication until spontaneous conversion is

achieved, with the possibility of cardioversion within 48 hours after onset of symptoms. Primary end point is the presence of sinus rhythm on 12-lead electrocardiogram at 4 weeks; main secondary outcomes are adverse events, total medical and societal costs, quality of life, and cost-effectiveness for 1 year.
**Conclusions:** The ACWAS trial aims at providing evidence for the use of a wait-and-see approach for patients with recent-onset symptomatic AF in the emergency department.

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Impact factor: 4.436

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**5. Long-term mortality and prehospital tirofiban treatment in patients with ST elevation myocardial infarction**
Fabris E, Kilic S, Schellings DAAM, Ten Berg JM, Kennedy MW, van Houwelingen KG, Giannitsis E, Kolkman E, Ottervanger JP, Hamm C, Van't Hof AWJ

**Objective:** We undertook a subgroup analysis of the On-TIME 2 (Ongoing Tirofiban In Myocardial infarction Evaluation 2), a placebo-controlled, double-blind, randomised trial, in order to evaluate the association between N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and long-term (5 years) mortality and to investigate the effect of prehospital tirofiban administration on mortality in relation to NT-proBNP levels.
**Methods:** A total of 984 patients with ST elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) were randomised to either in ambulance tirofiban or placebo. NT-proBNP levels were evaluated on admission before angiography (baseline) and 18-96 hours thereafter (post PCI).
**Results:** There were 918 (93.3%) patients with NT-proBNP values available at baseline and 865 (87.9%) post PCI. Patients with baseline NT-proBNP values above the median (137 pg/mL) had higher 30-day (5.1% vs 0.2%, p<0.001), 1-year (7.0% vs 0.7%, p<0.001) and 5-year (20.3% vs 4.9%, p<0.001) mortality as compared with patients with values below the median. Using multivariate Cox analysis, NT-proBNP above the median was an independent predictor for 5-year mortality (HR 2.73, 95% CI 1.47 to 5.06; p=0.002). Patients with values above the median who received early tirofiban treatment had significant lower mortality compared with patients treated with placebo at 30 days (2.7% vs 7.5%, p=0.021) and 1 year (4.5% vs 9.4%, p=0.043). At 5 years, a lower but non-significant mortality rate was maintained in the treatment group (18% vs 22.4%, p=0.265).
**Conclusions:** In patients with STEMI, baseline NT-proBNP level independently predicts long-term mortality. In patients with baseline NT-proBNP levels above the median, early prehospital treatment with tirofiban significantly reduced 30-day and 1-

year mortality, suggesting that high-risk patients may derive particular benefit. This finding should be confirmed in other studies. TRIAL REGISTRATION NUMBER: ISRCTN06195297.

Gepubliceerd: Heart 2017 Oct;103(19):1515-20
Impact factor: 6.059

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**6. Long-term Safety and Efficacy of New-Generation Drug-Eluting Stents in Women With Acute Myocardial Infarction: From the Women in Innovation and Drug-Eluting Stents (WIN-DES) Collaboration**
Giustino G, Harari R, Baber U, Sartori S, Stone GW, Leon MB, Windecker S, Serruys PW, Kastrati A, von Birgelen C, Kimura T, Stefanini GG, Dangas GD, Wijns W, Steg PG, Morice MC, Camenzind E, Weisz G, Smits PC, Sorrentino S, Sharma M, Farhan S, Faggioni M, Kandzari D, Galatius S, Jeger RV, Valgimigli M, Itchhaporia D, Mehta L, Kim HS, Chieffo A, Mehran R

**Importance:** Women with acute myocardial infarction (MI) undergoing mechanical reperfusion remain at increased risk of adverse cardiac events and mortality compared with their male counterparts. Whether the benefits of new-generation drug-eluting stents (DES) are preserved in women with acute MI remains unclear.
**Objective:** To investigate the long-term safety and efficacy of new-generation DES vs early-generation DES in women with acute MI.
**Design, Setting, and Participants:** Collaborative, international, individual patient-level data of women enrolled in 26 randomized clinical trials of DES were analyzed between July and December 2016. Only women presenting with an acute coronary syndrome were included. Study population was categorized according to presentation with unstable angina (UA) vs acute MI. Acute MI included non-ST-segment elevation MI (NSTEMI) or ST-segment elevation MI (STEMI). Interventions: Randomization to early- (sirolimus- or paclitaxel-eluting stents) vs new-generation (everolimus-, zotarolimus-, or biolimus-eluting stents) DES. Main Outcomes and Measures: Composite of death, MI or target lesion revascularization, and definite or probable stent thrombosis at 3-year follow-up.
**Results:** Overall, the mean age of participants was 66.8 years. Of 11577 women included in the pooled data set, 4373 (37.8%) had an acute coronary syndrome as clinical presentation. Of these 4373 women, 2176 (49.8%) presented with an acute MI. In women with acute MI, new-generation DES were associated with lower risk of death, MI or target lesion revascularization (14.9% vs 18.4%; absolute risk difference, -3.5%; number needed to treat [NNT], 29; adjusted hazard ratio, 0.78; 95% CI, 0.61-0.99), and definite or probable stent thrombosis (1.4% vs 4.0%; absolute risk difference, -2.6%; NNT, 46; adjusted hazard ratio, 0.36; 95% CI, 0.19-0.69) without evidence of interaction

for both end points compared with women without acute MI (P for interaction = .59 and P for interaction = .31, respectively). A graded absolute benefit with use of new-generation DES was observed in the transition from UA, to NSTEMI, and to STEMI (for death, MI, or target lesion revascularization: UA, -0.5% [NNT, 222]; NSTEMI, -3.1% [NNT, 33]; STEMI, -4.0% [NNT, 25] and for definite or probable ST: UA, -0.4% [NNT, 278]; NSTEMI, -2.2% [NNT, 46]; STEMI, -4.0% [NNT, 25]).
**Conclusions and Relevance:** New-generation DES are associated with consistent and durable benefits over 3 years in women presenting with acute MI. The magnitude of these benefits appeared to be greater per increase in severity of acute coronary syndrome.

Gepubliceerd: JAMA Cardiol 2017 Aug 1;2(8):855-62
Impact factor: 0

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**7. Comparison of Left Ventricular Function and Myocardial Infarct Size Determined by 2-Dimensional Speckle Tracking Echocardiography in Patients With and Without Chronic Obstructive Pulmonary Disease After ST-Segment Elevation Myocardial Infarction**
Goedemans L, Abou R, Hoogslag GE, Ajmone MN, Taube C, Delgado V, Bax JJ

Patients with chronic obstructive pulmonary disease (COPD) have a high risk of mortality after acute ST-segment elevation myocardial infarction (STEMI). We compared STEMI patients with versus without COPD in terms of infarct size and left ventricular (LV) systolic function using advanced 2-dimensional speckle tracking echocardiography. Of 1,750 patients with STEMI (mean age 61 +/- 12 years, 76% male), 133 (7.6%) had COPD. With transthoracic echocardiography, left ventricular ejection fraction (LVEF) and wall motion score index were measured. Infarct size was assessed using biomarkers (creatine kinase and troponin T). LV global longitudinal strain (GLS), reflecting active LV myocardial deformation, was measured with 2-dimensional speckle tracking echocardiography to estimate LV systolic function and infarct size. STEMI patients with COPD were significantly older, more likely to be former smokers, and had worse renal function compared with patients without COPD. There were no differences in infarct size based on peak levels of creatine kinase (1315 [613 to 2181] vs 1477 [682 to 3047] U/l, p = 0.106) and troponin T (3.3 [1.4 to 7.3] vs 3.9 [1.5 to 7.8] microg/l, p = 0.489). Left ventricular ejection fraction (46% vs 47%, p = 0.591) and wall motion score index (1.38 [1.25 to 1.66] vs 1.38 [1.19 to 1.69], p = 0.690) were comparable. In contrast, LV GLS was significantly more impaired in patients with COPD compared with patients without COPD (-13.9 +/- 3.0% vs -14.7 +/- 3.9%, p = 0.034). In conclusion, despite comparable myocardial infarct size and LV systolic function as assessed with biomarkers and conventional

echocardiography, patients with COPD exhibit more impaired LV GLS on advanced echocardiography than patients without COPD, suggesting a greater functional impairment at an early stage after STEMI.

Gepubliceerd: Am J Cardiol 2017 Sep 1;120(5):734-9
Impact factor: 3.398

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**8. Detection of elevated pulmonary pressures by the ECG-derived ventricular gradient: A comparison of conversion matrices in patients with suspected pulmonary hypertension**
Haeck ML, Kapel GF, Scherptong RW, Swenne CA, Maan AC, Bax JJ, Schalij MJ, Vliegen HW

**Background:** The aim was to assess the diagnostic value of the Inverse Dower (INVD)-derived vectorcardiogram (VCG) and the Kors-derived VCG to detect elevated systolic pulmonary artery pressure (SPAP) in suspected pulmonary hypertension (PH).
**Methods:** In 132 patients, morphologic variables were evaluated by comparing the VCG parameters synthesized by INVD and Kors matrix. Comparison of the diagnostic accuracy of detecting SPAP >/=50mmHg between the matrices was performed by ROC curve analysis and logistic regression analysis.
**Results:** Most VCG parameters differed significantly between INVD and Kors. ROC analysis for detection of SPAP >/=50mmHg by VG projected on the X-axis demonstrated no difference (p=0.99) between INVD (AUC=0.80) and Kors (AUC=0.80). Both the INVD- and Kors-derived VCG provided significant diagnostic information on the presence of SPAP >/=50mmHg (INVD, OR 1.05, 95%CI 1.03-1.07; P<0.001; Kors, OR 1.05, 95%CI 1.03-1.08; P<0.001).
**Conclusion:** Although there were significant differences in measures of vector morphology, both.

Gepubliceerd: J Electrocardiol 2017;50(1):115-22
Impact factor: 1.514

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**9. Sustained safety and clinical performance of a drug-eluting absorbable metal scaffold up to 24 months: pooled outcomes of BIOSOLVE-II and BIOSOLVE-III**
Haude M, Ince H, Kische S, Abizaid A, Tolg R, Alves Lemos P, Van Mieghem NM, Verheye S, von Birgelen C, Christiansen EH, Wijns W, Garcia-Garcia HM, Waksman R

**Aims:** We aimed to assess the safety and performance of the DREAMS 2G scaffold up to 24 months post implant.
**Methods and Results:** The present study population comprises a total of 184 patients with 189 lesions who were enrolled in the prospective, multicentre BIOSOLVE-II and BIOSOLVE-III trials. Clinical follow-up was scheduled at one, six, 12, 24 and 36 months. The present report includes pooled follow-up data at six months and BIOSOLVE-II data at 24 months. Patients were 65.5+/-10.8 years old, and lesions were 12.5+/-5.1 mm long with reference diameters of 2.7+/-0.4 mm. Procedural success was obtained in 97.8%. At six months, the composite clinical endpoint target lesion failure was 3.3% (95% CI: 1.2-7.1), based on two cardiac deaths (1.1%, one unknown and one not device-related), one target vessel myocardial infarction (0.6%), and three clinically driven target lesion revascularisations (1.7%). For BIOSOLVE-II at 24 months, the target lesion failure rate was 5.9% (95% CI: 2.4-11.8), based on two cardiac deaths (1.7%), one target vessel myocardial infarction (0.9%) and four target lesion revascularisations (3.4%). There was no definite or probable scaffold thrombosis.
**Conclusions:** The present analysis provides additional evidence on the safety of a drug-eluting absorbable metal scaffold with promising clinical outcomes up to 24 months and absence of definite or probable scaffold thrombosis.

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Impact factor: 5.193

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**10. Two-year outcome after treatment of severely calcified lesions with newer-generation drug-eluting stents in acute coronary syndromes: A patient-level pooled analysis from TWENTE and DUTCH PEERS**
Huisman J, van der Heijden LC, Kok MM, Louwerenburg JH, Danse PW, Jessurun GA, de Man FH, Lowik MM, Linssen GC, IJzerman MJ, Doggen CJ, von Birgelen C

**Background:** Data on medium-term outcome of patients with acute coronary syndrome (ACS), treated with newer-generation durable polymer drug-eluting stents (DES) in severely calcified coronary lesions, are scarce. We aimed to assess the impact of severe coronary lesion calcification on clinical outcome of patients with ACS, treated with newer-generation DES.
**Methods:** The TWENTE and DUTCH PEERS randomized trials comprise 1779 ACS patients, who were categorized into patients with versus without severe target lesion calcification. We performed a patient-level pooled analysis to assess 2-year outcome, including target vessel failure (TVF), a composite of cardiac death, target vessel-related myocardial infarction (MI), or target vessel revascularization (TVR).

**Results:** Patients with severe target lesion calcification (n=340, 19.1%) were older (66.8+/-10.6 years vs. 62.8+/-11.5 years, p<0.001) and had more often diabetes (22.1% vs. 16.8%, p=0.02) and hypercholesterolemia (51.5% vs. 42.9%, p=0.005) than other patients (n=1439, 79.9%). In addition they showed a higher TVF rate (12.4% vs.7.0%, p=0.001), mainly related to a difference in TVR (6.8% vs. 3.3%, p=0.003). There was a borderline significant between-group difference in cardiac death (3.6% vs. 1.8%, p=0.05), but not in target vessel MI (3.8% vs.2.6%, p=0.23) and definite stent thrombosis (0.9% vs. 0.6%, p=0.71). Multivariate analysis demonstrated that severe lesion calcification was an independent risk factor of TVF (adjusted HR; 1.58, 95% CI: 1.23-2.03; p<0.001).
**Conclusions:** In patients with ACS, treatment of severely calcified lesions with newer-generation DES was associated with an overall higher clinical event risk - related in particular to a higher TVR rate, while the risk of MI was low.

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Impact factor: 2.732

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**11. Relationship Between Myocardial Function, Body Mass Index, and Outcome After ST-Segment-Elevation Myocardial Infarction**
Joyce E, Hoogslag GE, Kamperidis V, Debonnaire P, Katsanos S, Mertens B, Marsan NA, Bax JJ, Delgado V

**Background:** Better survival for overweight and obese patients after ST-segment-elevation myocardial infarction (STEMI) has been demonstrated. The association between body mass index (BMI), outcome, and left ventricular (LV) structure and function after STEMI, including LV longitudinal strain (global longitudinal strain), was evaluated.
**Methods and Results:** First patients with STEMI undergoing primary percutaneous coronary intervention (n=1604; mean age, 61+/-12 years; 75% men) had BMI measured on admission, and 2-dimensional transthoracic echocardiography performed within 48 hours. Patients were categorized based on standard criteria (normal/underweight, BMI<25 kg/m2 [n=486]; overweight, 25</=BMI<30 kg/m2 [n=820]; obese, BMI>/=30 kg/m2 [n=298]). LV global longitudinal strain was measured using speckle-tracking analysis. Primary outcome measure was all-cause mortality. Compared with normal/underweight patients, obese patients were younger and more likely to have diabetes mellitus, hypertension, and hyperlipidemia and have higher discharge blood pressures. Despite no significant differences in infarct size, obese patients had significantly more impaired LV global longitudinal strain (-13.7+/-3.8 versus -15.0+/-4.2% and -15.0+/-4.1%; P<0.001) compared with normal/underweight and overweight patients, respectively. Although

normal/underweight patients had the worst overall survival (log-rank P=0.04) after STEMI during a median follow-up of 5.2 (3.6, 6.9) years on Kaplan-Meier analysis, a significant nonlinear association between BMI and all-cause mortality across the range of BMI was seen, persisting after adjustment for age and sex.
**Conclusions:** Obese patients demonstrate greater adverse LV remodeling and more impaired LV deformation after STEMI compared with those with normal BMI, amid similar infarct characteristics. Normal weight patients continue to demonstrate the worst survival, suggesting that the potential nonadverse effect of higher BMI in this population is independent of LV function.

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Impact factor: 6.803

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**12. Clinical Outcomes After Percutaneous Coronary Intervention with the COMBO Stent versus Resolute Integrity and Promus Element Stents: A Propensity- Matched Analysis**
Kalkman DN, Kok MM, van der Heijden LC, Woudstra P, Beijk MA, Tijssen JG, von Birgelen C, de Winter RJ

**Aims:** The COMBO stent combines a sirolimus-elution with an endothelial progenitor cell- capturing layer to promote early endothelialization. There has not been a head-to-head comparison of this novel device with any other currently used drug-eluting stent (DES). We compare clinical outcome at 2-years after COMBO stent placement with the Resolute Integrity or Promus Element stent in an all-comers cohort.
**Methods and Results:** Patients from the REMEDEE Registry (COMBO, n=1000) were matched with patients from the DUTCH PEERS trial (Promus Element/Resolute Integrity, n=1811). Propensity score-matching on 13 baseline characteristics was applied to create two balanced cohorts of patients treated with COMBO versus Promus Element/Resolute Integrity. Propensity-score matching yielded 771 patient pairs, representing all-comers patients, with a median age of 65 years, 27% females and more than 50% of patients presenting with acute coronary syndrome. Target lesion failure (TLF, a composite of cardiac death, target vessel MI and any target lesion revascularization) at 2-year follow-up was 7.9% in COMBO and 6.4% in Promus Element/Resolute Integrity, HR 1.24 (95%-CI: 0.85-1.81), p=0.26. Definite stent thrombosis (ST) was not significantly different between groups (0.8% vs. 0.9%, p=0.79).
**Conclusions:** In a propensity-matched analysis; the COMBO stent shows similar rates of TLF and ST rates at 2-year follow-up, compared to Resolute Integrity and Promus Element.

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Impact factor: 5.193

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**13. Endothelial function after ST-elevation myocardial infarction in patients with high levels of high-sensitivity CRP and Lp-PLA2: A substudy of the RESPONSE randomized trial**

Kandhai-Ragunath JJ, de Wagenaar B, Doelman C, van Es J, Jorstad HT, Peters RJG, Doggen CJM, von Birgelen C

**Background:** The combination of high levels of high-sensitive C-reactive protein (hs-CRP) and lipoprotein-associated phospholipase-A2 (Lp-PLA2) was recently shown to correlate with increased cardiovascular risk. Endothelial dysfunction is also known to be a risk factor for cardiovascular events. AIM: To test among patients with previous ST-elevation myocardial infarction (STEMI) the hypothesis that high levels of both hs-CRP and Lp-PLA2 may be associated with impaired endothelium-dependent vasodilatation.
**Methods:** In this substudy of the RESPONSE randomized trial, we used reactive hyperemia peripheral artery tonometry (RH-PAT) 4 to 6weeks after STEMI and primary percutaneous coronary intervention (PPCI) to non-invasively assess endothelial function (RH-PAT index <1.67 identified endothelial dysfunction). Reliable measurements of RH-PAT, hs-CRP, and Lp-PLA2 were obtained in 68 patients, who were classified as high-risk if levels of both hs-CRP and Lp-PLA2 were in the upper tertile (>/=3.84mg/L and >239mug/L, respectively).
**Results:** Patients were 57.4+/-9.7years and 53 (77.9%) were men. 11 (16%) patients were classified as high-risk and 57 (84%) as low-to-intermediate-risk. The RH-PAT index was 1.68+/-0.22 in high-risk and 1.95+/-0.63 in low-to-intermediate-risk patients (p=0.17). Endothelial dysfunction was present in 8 (72.7%) high-risk and 26 (45.6%) low-to-intermediate-risk patients (p=0.09). Framingham risk score, NT-proBNP and fibrinogen levels were higher in high-risk patients (p</=0.03).
**Conclusion:** In this population of patients with recent STEMI and PPCI, we observed between patients with high hs-CRP and Lp-PLA levels and all other patients no more than numerical differences in endothelial function that did not reach a statistical significance. Nevertheless, further research in larger study populations may be warranted.

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Impact factor: 0

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**14. Arrhythmogenic anatomical isthmuses identified by electroanatomical mapping are the substrate for ventricular tachycardia in repaired tetralogy of Fallot**
Kapel GF, Sacher F, Dekkers OM, Watanabe M, Blom NA, Thambo JB, Derval N, Schalij MJ, Jalal Z, Wijnmaalen AP, Zeppenfeld K

**Aims:** The majority of ventricular tachycardias (VTs) in repaired tetralogy of Fallot (rTOF) are related to anatomically defined isthmuses. We aimed to identify specific electroanatomical characteristics of anatomical isthmuses (AI) related to VT which may allow for individualized risk stratification and tailored ablation.
**Methods and Results:** Seventy-four consecutive rTOF patients (40 +/- 16 years, 63% male) underwent VT induction and right ventricular electroanatomical voltage and activation mapping during sinus rhythm (SR) to identify the presence and characteristics of AI (isthmus width, length and conduction velocity index [CVi]). Twenty-eight patients were inducible for 41 VTs. All 74 patients had at least one AI. However, AI in patients with VT were longer (22 +/- 7 vs. 16 +/- 7 mm, P = 0.001), narrower (20 +/- 8 vs. 28 +/- 11 mm, P < 0.001) and had lower CVi (0.36 +/- 0.34 vs. 0.78 +/- 0.24 m/s, P < 0.001). Thirty-seven VTs in 24 patients were mapped (pace-, entrainment mapping, and/or VT termination by ablation) to 28 AI. All 28 AI related to VT had a CVi < 0.5 m/s (slow conducting AI (SCAI)). In contrast, 87 of 89 AI of the 46 patients without VT had CVi >/= 0.5 m/s. Sixty-two patients were discharged without the presence of an SCAI (44 had no SCAI at baseline, 18 underwent ablation of the SCAI) and 10 still had an SCAI (no/failed ablation). During follow-up (50 +/- 22 months), no patient without SCAI had any VT, which occurred in 5/10 patients with SCAI (P < 0.001).
**Conclusion:** In rTOF, slow conducting anatomical isthmuses identified by electroanatomical mapping during SR are the dominant substrate for VT allowing individualized risk stratification and preventive ablation.

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**15. A prospective, randomized, open-label trial of 6-month versus 12-month dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction: Rationale and design of the "DAPT-STEMI trial"**
Kedhi E, Fabris E, van der Ent M, Kennedy MW, Buszman P, von Birgelen C, Cook S, Wedel H, Zijlstra F

**Background:** The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention with second-generation drug eluting stents

(DESs) is unclear. Because prolonged DAPT is associated with higher bleeding risk and health care costs, establishing optimal DAPT duration is of paramount importance. No other randomized controlled trials have evaluated the safety of shorter DAPT duration in ST-elevation myocardial infarction (STEMI) patients treated with second-generation DESs and latest P2Y12 platelet receptor inhibitors.
**Hypothesis:** Six months of DAPT after Resolute Integrity stent implantation in STEMI patients is not inferior to 12 months of DAPT in clinical outcomes. STUDY
**Design:** The Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation In ST-elevation Myocardial Infarction (DAPT-STEMI) trial is a randomized, multicenter, international, open-label trial designed to examine the safety (noninferiority) of 6-month DAPT after Resolute Integrity stent implantation in STEMI patients compared with 12-month DAPT. Event-free patients on DAPT at 6month will be randomized (1:1 fashion) between single (aspirin only) versus DAPT for an additional 6 months and followed until 2 years after primary percutaneous coronary intervention. The primary end point is a patient-oriented composite endpoint of all-cause mortality, any myocardial infarction, any revascularization, stroke, and major bleeding (net adverse clinical events [NACE]) at 18 months after randomization. To achieve a power of 85% for a noninferiority limit of 1.66, a total of 1100 enrolled patients are required.
**Summary:** The DAPT-STEMI trial aims to assess in STEMI patients treated with second-generation DESs whether discontinuation of DAPT after 6 months of event-free survival is noninferior to routine 12-month DAPT.

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Impact factor: 4.436

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**16. Incidence, risk factors, and predictors of infective endocarditis in adult congenital heart disease: focus on the use of prosthetic material**
Kuijpers JM, Koolbergen DR, Groenink M, Peels KCH, Reichert CLA, Post MC, Bosker HA, Wajon EMCJ, Zwinderman AH, Mulder BJM, Bouma BJ

**Aims:** Adult congenital heart disease (ACHD) predisposes to infective endocarditis (IE). Surgical advancements have changed the ACHD population, whereas associated prosthetic material may constitute additional IE targets. We aimed to prospectively determine contemporary incidence, risk factors, and predictors of IE in a nationwide ACHD cohort, focusing on the presence of prosthetics.

**Methods and results:** We identified 14 224 patients prospectively followed in the CONCOR ACHD registry (50.5% female, median age 33.6years). IE incidence was determined using Poisson regression, risk factors and predictors using Cox regression. Overall incidence was 1.33 cases/1000 person-years (124 cases in 93

562 person-years). For risk-factor analysis, presence of prosthetics was forced-as separate time-updated variables for specific prosthetics-into a model with baseline characteristics univariably associated with IE. Valve-containing prosthetics were independently associated with greater risk both short- and long term after implantation [0-6 months: hazard ratio (HR) = 17.29; 7.34-40.70, 6-12 months: HR = 15.91; 6.76-37.45, beyond 12 months: HR = 5.26; 3.52-7.86], non-valve-containing prosthetics, including valve repair, only in the first 6 months after implantation (HR = 3.34; 1.33-8.41), not thereafter. A prediction model was derived and validated using bootstrapping techniques. Independent predictors of IE were baseline valve-containing prosthetics, main congenital heart defect, multiple defects, previous IE, and sex. The model had fair discriminative ability and provided accurate predictions up to 10 years.
**Conclusions:** This study provides IE incidence estimates, and determinants of IE risk in a nationwide ACHD cohort. Our findings, essentially informing IE prevention guidelines, indicate valve-containing prosthetics as a main determinant of IE risk whereas other prosthetics, including valve-repair, are not associated with increased risk long term after implantation.

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Impact factor: 20.212

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**17. Use of three-dimensional computed tomography overlay for real-time cryoballoon ablation in atrial fibrillation reduces radiation dose and contrast dye**

Oude Velthuis B, Molenaar MMD, Reinhart Dorman HG, Stevenhagen JY, Scholten MF, van der Palen J, van Opstal JM

**Aims:** Cryoballoon pulmonary vein (PV) isolation in patients with atrial fibrillation has proven to be effective in short-term and long-term follow-up. To visualise the PV anatomy, pre-ablation contrast pulmonary venography is commonly performed. Three-dimensional (3D) computed tomography (CT) overlay is a new technique creating a live 3D image of the left atrium by integrating a previously obtained CT scan during fluoroscopy. To evaluate the benefits of 3D CT overlay during cryoballoon ablation, we studied the use of 3D CT overlay versus contrast pulmonary venography in a randomised fashion in patients with paroxysmal atrial fibrillation undergoing cryoballoon PV isolation.
**Methods and Results:** Between October 2012 and June 2013, 30 patients accepted for PV isolation were randomised to cryoballoon PV isolation using either 3D CT overlay or contrast pulmonary venography. All patients underwent a pre-procedural cardiac CT for evaluation of the anatomy of the left atrium (LA) and the PVs. In the 3D

CT overlay group, a 3D reconstruction of the LA and PVs was made. An overlay of the CT reconstruction was then projected over live fluoroscopy. Patients in the contrast pulmonary venography group received significantly more contrast agent (77.1 +/- 21.2 cc vs 40.1 +/- 17.6 cc, p < 0.001) and radiation (43.0 +/- 21.9 Gy.cm2 vs 28.41 +/- 11.7 Gy.cm2, p = 0.04) than subjects in the 3D CT overlay group. There was no difference in total procedure time, fluoroscopy time and the amount of cryoapplications between the two groups.
**Conclusion:** The use of 3D CT overlay decreases radiation and contrast dye exposure and can assist in guiding cryoballoon-based PV isolation.

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Impact factor: 1.894

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**18. Rehospitalizations Following Primary Percutaneous Coronary Intervention in Patients With ST-Elevation Myocardial Infarction: Results From a Multi-Center Randomized Trial**
Spitzer E, Frei M, Zaugg S, Hadorn S, Kelbaek H, Ostojic M, Baumbach A, Tuller D, Roffi M, Engstrom T, Pedrazzini G, Vukcevic V, Magro M, Kornowski R, Luscher TF, von Birgelen C, Heg D, Windecker S, Raber L

**Background:** Rehospitalizations (RHs) after ST-elevation myocardial infarction carry a high economic burden and may deteriorate quality of life. Characterizing patients at higher risk may allow the design of preventive measures. We studied the frequency, reasons, and predictors for unplanned cardiac and noncardiac RHs in ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention.
**Methods and Results:** In this post-hoc analysis of the COMFORTABLE AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction; NCT00962416) trial including 1137 patients, unplanned cardiac and noncardiac RHs occurred in 133 (11.7%) and in 79 patients (6.9%), respectively, at 1 year. The most frequent reasons for unplanned cardiac RHs were recurrent chest pain without evidence of ischemia (20.4%), recurrent chest pain with ischemia and coronary intervention (16.9%), and ischemic events (16.9%). Unplanned noncardiac RHs occurred most frequently attributed to bleeding (24.5%), infections (14.3%), and cancer (9.1%). On multivariate analysis, left ventricular ejection fraction (22% increase in the rate of RHs per 10% decrease; P=0.03) and angiographic myocardial infarction Syntax score (34% increase per 10-point increase; P=0.01) were independent predictors of unplanned cardiac RHs. Age emerged as the only independent predictor of unplanned noncardiac RHs. Regional differences for unplanned cardiac RHs were observed.

**Conclusions:** Among ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention in the setting of a randomized, clinical trial, unplanned cardiac RHs occurred in 12% with recurrent chest pain being the foremost reason. Unplanned noncardiac RHs occurred in 7% with bleeding as the leading cause. Left ventricular ejection fraction and Syntax score were independent predictors of unplanned cardiac RHs and identified patient subgroups in need for improved secondary prevention. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT00962416.

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Impact factor: 5.117

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**19. First-in-man six-month results of a surface-modified coronary stent system in native coronary stenosis**

Suwannasom P, Sotomi Y, Corti R, Kurz DJ, Roffi M, von Birgelen C, Buzzi S, Zucker A, Dijkstra J, Wykrzykowska JJ, de Winter RJ, Windecker S, Onuma Y, Serruys PW, Daemen J, Raber L

**Aims:** In preclinical studies, a bare metal cobalt-chromium stent with an active surface oxide layer modification (BMSmod) has been shown to inhibit neointimal hyperplasia effectively. We sought to assess both the clinical safety and feasibility of the BMSmod.
**Methods and Results:** In this prospective, non-randomised, first-in-man multicentre study, a total of 31 patients with de novo coronary lesions, reference lumen diameters of 2.5-3.5 mm and lesion length </=16 mm, were enrolled. Quantitative coronary angiography and optical coherence tomography (OCT) were performed at baseline and six-month follow-up. Primary angiographic and OCT endpoints included in-stent late lumen loss (LLL) and mean neointimal thickness at six months. The device-oriented composite endpoint (DoCE), defined as cardiac death, myocardial infarction not clearly attributable to a non-intervention vessel, and clinically indicated target lesion revascularisation (CI-TLR), was analysed according to the intention-to-treat principle. In 31 patients (33 lesions), the procedural success rate was 93.5%. At six months, angiographic LLL was 0.91+/-0.45 mm and binary angiographic restenosis occurred in 23.3% of lesions. Out of 33 lesions, OCT was performed in 27 lesions at both time points. Mean neointimal thickness amounted to 348+/-116 microm. At six months, the DoCE was 19.4% due to the occurrence of CI-TLR in five patients (including one late definite stent thrombosis of a non-study stent).
**Conclusions:** In contrast to previous preclinical pathophysiological work, the BMSmod did not prevent neointimal hyperplasia in a first-in-man clinical setting.

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**20. Dutch outcome in implantable cardioverter-defibrillator therapy (DO-IT): registry design and baseline characteristics of a prospective observational cohort study to predict appropriate indication for implantable cardioverter-defibrillator**

van Barreveld M, Dijkgraaf MGW, Hulleman M, Boersma LVA, Delnoy PPHM, Meine M, Tuinenburg AE, Theuns DAMJ, van der Voort PH, Kimman GP, Buskens E, Tijssen JPG, Bruinsma N, Verstraelen TE, Zwinderman AH, van Dessel PHFM, Wilde AAM

**Background:** Implantable cardioverter-defibrillators (ICDs) are widely used for the prevention of sudden cardiac death. At present, both clinical benefit and cost-effectiveness of ICD therapy in primary prevention patients are topics of discussion, as only a minority of these patients will eventually receive appropriate ICD therapy.
**Methods/Design:** The DO-IT Registry is a nationwide prospective cohort with a target enrolment of 1,500 primary prevention ICD patients with reduced left ventricular function in a setting of structural heart disease. The primary outcome measures are death and appropriate ICD therapy for ventricular tachyarrhythmias. Secondary outcome measures are inappropriate ICD therapy, death of any cause, hospitalisation for ICD related complications and for cardiovascular reasons. As of December 2016, data on demographic, clinical, and ICD characteristics of 1,468 patients have been collected. Follow-up will continue up to 24 months after inclusion of the last patient. During follow-up, clinical and ICD data are collected based on the normal follow-up of these patients, assuming ICD interrogations take place every six months and clinical follow-up is once a year. At baseline, the mean age was 66 (standard deviation [SD] 10) years and 27% were women.
**Conclusion:** The DO-IT Registry represents a real-world nationwide cohort of patients receiving ICDs for primary prevention of sudden cardiac death with reduced left ventricular function in a setting of structural heart disease. The registry investigates the efficacy of the current practice and aims to develop prediction rules to identify subgroups who will not (sufficiently) benefit from ICD implantation and to provide results regarding costs and budget impact of targeted supply of primary preventions ICDs.

Gepubliceerd: Neth Heart J 2017 Aug 7;25(10):574-80
Impact factor: 1.894

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**21. Three-Year Clinical Outcome of Patients with Coronary Disease and Increased Event Risk Treated with Newer-Generation Drug-Eluting Stents: From the Randomized DUTCH PEERS Trial**
van der Heijden LC, Kok MM, Lowik MM, Danse PW, Jessurun GAJ, Hartmann M, Stoel MG, van Houwelingen KG, Hautvast RWM, Linssen GC, Doggen CJM, von Birgelen C

**Objective:** Limited data is available on the long-term outcome of patients with increased cardiovascular event risk, treated with newer-generation durable polymer drug-eluting stents (DES).
**Methods:** We therefore assessed 3-year follow-up data of high-risk versus low- to intermediate-risk patients of the randomized DUTCH PEERS trial (NCT01331707). In both risk groups we also compared patients treated with Resolute Integrity versus Promus Element DES. Patients were categorized as "high-risk" if they met >/=1 of the following criteria: (1) diabetes (17.9%); (2) previous myocardial infarction (21.9%); (3) previous coronary revascularization (25.8%); (4) chronic renal failure (3.5%); (5) left ventricular ejection fraction </=30% (1.5%); and (6) age >/=75 years (17.3%).
**Results:** At the 3-year follow-up, the incidence of the composite endpoint target vessel failure (TVF) (13.2 vs. 7.5%; logrank p < 0.001) and 2 of its components - cardiac death (4.7 vs. 1.5%; logrank p < 0.001) and target vessel revascularization (7.3 vs. 4.7%; logrank p = 0.03) - was higher in high-risk (n = 957) versus low- to intermediate-risk patients (n = 854). Among high-risk patients, treatment with Resolute Integrity (n = 481) and Promus Element stents (n = 476) was similarly safe and efficacious (TVF: 13.3 vs. 13.1%; logrank p = 0.95; definite-or-probable stent thrombosis: 1.7 vs. 1.7%; logrank p = 1.00).
**Conclusions:** The newer-generation Resolute Integrity and Promus Element stents showed similar results in terms of safety and efficacy for treating high-risk patients, who had significantly higher event rates than patients with low-to-intermediate risk.

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Impact factor: 1.742

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**22. Three-year safety and efficacy of treating all-comers with newer-generation Resolute Integrity or PROMUS Element stents in the randomised DUTCH PEERS (TWENTE II) trial**
van der Heijden LC, Kok MM, Lowik MM, Danse PW, Jessurun GAJ, Hautvast RWM, van Houwelingen KG, Stoel MG, Hartmann M, Linssen GC, Doggen CJM, von Birgelen C

**Aims:** The aim of this report was to assess the three-year safety and efficacy of implanting newer-generation Resolute Integrity zotarolimus-eluting stents (ZES) versus PROMUS Element everolimus-eluting stents (EES) in all-comers.
**Methods and Results:** In the randomised, multicentre, investigator-initiated DUTCH PEERS trial, a total of 1,811 all-comers were 1:1 randomly assigned to treatment with ZES versus EES. A total of 1,293 patients (72%) were treated for complex lesions and 455 patients (25%) were treated for multiple lesions. The primary endpoint target vessel failure (TVF) is a composite of cardiac death, target vessel-related myocardial infarction or target vessel revascularisation. Adverse clinical events were independently adjudicated. Three-year follow-up data were obtained in 1,807 patients (99.8%, four withdrawals). Both the ZES and EES groups showed favourable outcomes with a similar incidence of TVF (10.7% vs. 10.3%; pLog-rank=0.77) and the individual components thereof: cardiac death (3.2% vs. 3.1%; pLog-rank=0.87), target vessel-related myocardial infarction (2.8% vs. 2.2%; pLog-rank=0.44) and target vessel revascularisation (6.0% vs. 6.2%; pLog-rank=0.87). In addition, the incidence of definite or probable stent thrombosis was similar for patients treated with ZES versus EES (1.4% vs. 1.1%; pLog-rank=0.66).
**Conclusions:** The safety and efficacy of treating all-comers with newer-generation Resolute Integrity and PROMUS Element stents was found to be extended up to three years.

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Impact factor: 5.193

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**23. Prognostic Value of Serial Galectin-3 Measurements in Patients With Acute Heart Failure**
van Vark LC, Lesman-Leegte I, Baart SJ, Postmus D, Pinto YM, de Boer RA, Asselbergs FW, Wajon EMCJ, Orsel JG, Boersma E, Hillege HL, Akkerhuis KM

**Background:** Several clinical studies have evaluated the association between galectin-3 levels and outcome in patients with heart failure (HF). However, little is known about the predictive value of repeated galectin-3 measurements. This study evaluates the prognostic value of repeated time-dependent galectin-3 measurements in acute HF patients.
**Methods and Results:** In the TRIUMPH (Translational Initiative on Unique and Novel Strategies for Management of Patients with Heart Failure) clinical cohort study, 496 acute HF patients were enrolled in 14 hospitals in The Netherlands, between 2009 and 2014. Repeated blood samples (7) were drawn during 1-year follow-up. Associations between repeated biomarker measurements and the primary end point were assessed using a joint model. Median age was 74 years and 37% were women.

The primary end point, composite of all-cause mortality and HF rehospitalization, was reached in 188 patients (40%), during a median follow-up of 325 days (interquartile range 85-401). The median baseline galectin-3 level was 24 ng/mL (interquartile range 18-34). The mean number of galectin-3 measurements available per patient was 4.3. After adjustment for clinical factors and N-terminal pro-brain natriuretic peptide, there was a weak association between baseline galectin-3 and risk of the primary end point. When repeated measurements were taken into account, the adjusted hazard ratio per 1 SD increase of the galectin-3 level (on the log2 scale) at any time point increased to 1.67 (95% confidence interval, 1.24-2.23, P<0.001). After additional adjustment for repeated N-terminal pro-brain natriuretic peptide measurements, the association remained statistically significant.
**Conclusions:** Repeated galectin-3 measurements appeared to be a strong predictor of outcome in acute HF patients, independent of N-terminal pro-brain natriuretic peptide. Hence, galectin-3 may be helpful in clinical practice for prognostication and treatment monitoring.

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Impact factor: 5.117

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**24. Isolated Subepicardial Right Ventricular Outflow Tract Scar in Athletes With Ventricular Tachycardia**
Venlet J, Piers SR, Jongbloed JD, Androulakis AF, Naruse Y, den Uijl DW, Kapel GF, de Riva M, van Tintelen JP, Barge-Schaapveld DQ, Schalij MJ, Zeppenfeld K

**Background:** High-level endurance training has been associated with right ventricular pathological remodeling and ventricular tachycardia (VT). Although overlap with arrhythmogenic right ventricular cardiomyopathy (ARVC) has been suggested, the arrhythmogenic substrate for VTs in athletes is unknown. OBJECTIVES: The goal of this study was to evaluate whether electroanatomic scar patterns related to sustained VT can distinguish exercise-induced arrhythmogenic remodeling from ARVC and post-inflammatory cardiomyopathies.
**Methods:** In 57 consecutive patients (mean age 48 +/- 16 years; 83% male) undergoing catheter ablation for scar-related right ventricular VT, 2 distinct scar distributions were identified: 1) scars involving the subtricuspid right ventricle in 46 patients (group A); and 2) scars restricted to the anterior subepicardial right ventricular outflow tract in 11 patients (group B).

**Results:** Definite ARVC or post-inflammatory cardiomyopathy was diagnosed in 40 (87%) of 46 group A patients but was not diagnosed in any patients in group B. All group B patients underwent intensive endurance training for a median of 15 h/week

(interquartile range [IQR]: 10 to 20 h/week) for a median of 13 years (IQR: 10 to 18 years). The cycle lengths of scar-related VTs were significantly faster in group B patients (257 +/- 34 ms vs. 328 +/- 72 ms in group A; p = 0.003). Catheter ablation resulted in complete procedural success in 10 (91%) of 11 group B patients compared with 26 (57%) of 46 group A patients (p = 0.034). During a median follow-up of 27 months (IQR: 6 to 62 months), 50% of group A patients but none of the group B patients had a VT recurrence.
**Conclusions:** This study describes a novel clinical entity of an isolated subepicardial right ventricular outflow tract scar serving as a substrate for fast VT in high-level endurance athletes that can be successfully treated by ablation. This scar pattern may allow distinguishing exercise-induced arrhythmogenic remodeling from ARVC and post-inflammatory cardiomyopathy.

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Impact factor: 19.896

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**25. Unipolar Endocardial Voltage Mapping in the Right Ventricle: Optimal Cutoff Values Correcting for Computed Tomography-Derived Epicardial Fat Thickness and Their Clinical Value for Substrate Delineation**
Venlet J, Piers SRD, Kapel GFL, de Riva M, Pauli PFG, van der Geest RJ, Zeppenfeld K

**Background:** Low endocardial unipolar voltage (UV) at sites with normal bipolar voltage (BV) may indicate epicardial scar. Currently applied UV cutoff values are based on studies that lacked epicardial fat information. This study aimed to define endocardial UV cutoff values using computed tomography-derived fat information and to analyze their clinical value for right ventricular substrate delineation.
**Methods and Results:** Thirty-three patients (50+/-14 years; 79% men) underwent combined endocardial-epicardial right ventricular electroanatomical mapping and ablation of right ventricular scar-related ventricular tachycardia with computed tomographic image integration, including computed tomography-derived fat thickness. Of 6889 endocardial-epicardial mapping point pairs, 547 (8%) pairs with distance <10 mm and fat thickness <1.0 mm were analyzed for voltage and abnormal (fragmented/late potential) electrogram characteristics. At sites with endocardial BV >1.50 mV, the optimal endocardial UV cutoff for identification of epicardial BV <1.50 mV was 3.9 mV (area under the curve, 0.75; sensitivity, 60%; specificity, 79%) and cutoff for identification of abnormal epicardial electrogram was 3.7 mV (area under the curve, 0.88; sensitivity, 100%; specificity, 67%). The majority of abnormal electrograms (130 of 151) were associated with transmural scar. Eighty-six percent of abnormal epicardial electrograms had corresponding endocardial sites with BV <1.50

mV, and the remaining could be identified by corresponding low endocardial UV <3.7 mV.
**Conclusions:** For identification of epicardial right ventricular scar, an endocardial UV cutoff value of 3.9 mV is more accurate than previously reported cutoff values. Although the majority of epicardial abnormal electrograms are associated with transmural scar with low endocardial BV, the additional use of endocardial UV at normal BV sites improves the diagnostic accuracy resulting in identification of all epicardial abnormal electrograms at sites with <1.0 mm fat.

Gepubliceerd: Circ Arrhythm Electrophysiol 2017 Aug;10(8)
Impact factor: 5.410

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**26. Five-Year Outcome After Implantation of Zotarolimus- and Everolimus-Eluting Stents in Randomized Trial Participants and Nonenrolled Eligible Patients: A Secondary Analysis of a Randomized Clinical Trial**
von Birgelen C, van der Heijden LC, Basalus MW, Kok MM, Sen H, Louwerenburg HW, van Houwelingen KG, Stoel MG, de Man FH, Linssen GC, Tandjung K, Doggen CJ, van der Palen J, Lowik MM

**Importance:** Long-term follow-up after a clinical trial of 2 often-used, newer-generation drug-eluting stents (DESs) in a broad patient population is of interest. Comprehensive long-term outcome of eligible nonenrolled patients has never been reported.
**Objective:** To assess 5-year safety and efficacy of 2 newer-generation DESs in randomized participants with non-ST-elevation acute coronary syndromes or stable angina and to evaluate long-term outcomes of nonenrolled eligible patients treated with the same DESs.
**Design, Setting, and Participants:** The TWENTE (Real-World Endeavor Resolute vs Xience V Drug-Eluting Stent Study in Twente) trial is an investigator-initiated, patient-blinded, randomized, comparative DES trial that enrolled patients from June 18, 2008, to August 26, 2010. Most patients had non-ST-elevation acute coronary syndromes and complex lesions. Of all 1709 eligible patients, 1391 (81.4%) were treated in the TWENTE trial with zotarolimus-eluting (ZES, n = 697) or everolimus-eluting (EES, n = 694) cobalt-chromium stents. The remaining 318 eligible patients (18.6%) were not enrolled but underwent nonrandomized treatment with the same DESs. Data were analyzed from August 26, 2015, to October 11, 2016. Event rates (percentages) were derived from log-rank analysis and may differ from straightforward calculation (nominator/denominator). The 5-year follow-up of the TWENTE participants was prespecified in the trial protocol; that of the nonenrolled participants was ad hoc. Main Outcomes and Measures: Target vessel failure (TVF),

a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization.
**Results:** Of 1709 eligible participants, 1233 (72.1%) were men, 476 (27.9%) were women, and mean (SD) age was 64.6 (10.6) years. Among the 1370 of 1391 TWENTE trial participants (98.5% follow-up), TVF was similar between those in the ZES (16.1%) and EES (18.1%) groups (P = .36). Stent thrombosis rates were low: definite (7 of 697 [1.0%] vs 4 of 694 [0.6%]; P = .37) and occurred after more than 1 year in 3 (0.4%) with ZES vs 4 (0.6%) with EES (P = .69). The 318 nonenrolled eligible patients (308 patients [96.9%] of whom were followed up) were older and had more advanced disease than trial participants. Their TVF rate was higher than that of trial participants (71 of 318 [23.3%] vs 233 of 1391 [17.1%]; P = .02), which partly reflects a difference in cardiac mortality (23 of 318 [7.7%] vs 60 of 1391 [4.5%]; P = .03). Similar 5-year rates were found for myocardial infarction (91 of 1391 [6.7%] vs 22 of 318 [7.2%]; P = .80) and target vessel revascularization (129 of 1391 [9.7%] vs 34 of 318 [11.4%]; P = .36) between trial participants and nonenrolled eligible patients. In all eligible patients (ie, trial participants plus nonenrolled eligible patients), the TVF rate was only slightly higher than in trial participants only (18.3% vs 17.1%).
**Conclusions and Relevance:** Long-term outcome data from nonenrolled eligible patients support the validity of the TWENTE trial findings and present, with the trial, a strong case for the long-term safety and efficacy of the newer-generation DESs used.
Trial Registration: clinicaltrials.gov Identifier: NCT01066650.

Gepubliceerd: JAMA Cardiol 2017 Mar 1;2(3):268-76
Impact factor: 0

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**27. Reply to Letter to the Editor entitled: "Bioresorbable stent thrombosis, lactic acid release and Kounis syndrome"**
von Birgelen C, van der Heijden LC, Mukete BN

Int J Cardiol 2017 Nov 15;247:16
Impact factor: 6.189

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**28. A novel four-dimensional angiographic approach to assess dynamic superficial wall stress of coronary arteries in vivo: Initial experience in evaluating vessel sites with subsequent plaque rupture**
Wu X, von Birgelen C, Muramatsu T, Li Y, Holm NR, Reiber JH, Tu S

**Aims:** Repetitive and fluctuating stress is one important biomechanical mechanism that underlies the rupture of atherosclerotic plaques. We developed a novel coronary

angiography-based method for in vivo 4-dimensional analysis of dynamic superficial wall stress (SWS) in coronary plaques and applied it for the first time in two clinical cases to investigate the potential relationship between dynamic stress concentration at baseline and plaque rupture during acute coronary syndrome (ACS) several months later.
**Methods and Results:** Three-dimensional angiographic reconstructions of the interrogated arteries were performed at several phases of the cardiac cycle, followed by finite element analysis to obtain the dynamic SWS data. The peak stress at baseline was found at the distal and proximal lesion longitudinal shoulders, being 121.8kPa and 98.0kPa, respectively. Intriguingly, in both cases, the sites with the highest SWS concentration at baseline co-registered with the plaque ruptured location during ACS, respectively 6 and 18 months after the baseline angiographic assessment.
**Conclusions:** A novel angiography-based analysis method for 4-dimensional evaluation of dynamic SWS was feasible for investigating the plaque biomechanical behavior in vivo. Initial experience suggests that this technique could be useful in exploring mechanisms of future plaque rupture.

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Impact factor: 5.193

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**29. Superficial wall stress assessed from 4-D analysis of coronary angiography in vivo**
Wu X, von Birgelen C, Wijns W, Tu S

Int J Cardiovasc Imaging 2017 Jul;33(7):1111-2
Impact factor: 1.896

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**30. Current MitraClip experience, safety and feasibility in the Netherlands**
Rahhab Z, Kortlandt FA, Velu JF, Schurer RAJ, Delgado V, Tonino P, Boven AJ, Van den Branden BJL, Kraaijeveld AO, Voskuil M, Hoorntje J, van Wely M, van Houwelingen KG, Bleeker GB, Rensing B, Kardys I, Baan Jr. J, Van der Heyden JAS, Van Mieghem NM

**Purpose:** Data on MitraClip procedural safety and efficacy in the Netherlands are scarce. We aim to provide an overview of the Dutch MitraClip experience.
**Methods:** We pooled anonymised demographic and procedural data of 1151 consecutive MitraClip patients, from 13 Dutch hospitals. Data was collected by product specialists in collaboration with local operators. Effect on mitral regurgitation

was intra-procedurally assessed by transoesophageal echocardiography. Technical success and device success were defined according to modified definitions of the Mitral Valve Academic Research Consortium (MVARC).
**Results:** Median age was 76 (interquartile range 69-82) years and 59% were males. Patients presented with >/=moderate mitral regurgitation and a predominance of functional mitral regurgitation (72%). Overall, 611 (53%) patients were treated with one Clip, 486 (42%) with >/=2 Clips and 54 (5%) received no Clip. The number of patients with >/=2 Clips increased from 22% in 2009 to 52% in 2016. Device success and technical success were 91 and 95%, respectively, and were consistent over the years. Significant reduction of mitral regurgitation by MitraClip was achieved in 94% of patients and was observed more often in patients with functional mitral regurgitation (95% vs. 91%, p = 0.025). Device time declined from 145 min in 2009 to 55 min in 2016.
**Conclusion:** MitraClip experience in the Netherlands is growing with excellent technical success and device success. Over the years, device time decreased and more patients were treated with >/=2 Clips.

Gepubliceerd in: Neth Heart J 2017 Jun;25(6):394-400
Impact factor: 1.894

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**31. Implant and Midterm Outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry: The EFFORTLESS Study**
Boersma L, Barr C, Knops R, Theuns D, Eckardt L, Neuzil P, Scholten M, Hood M, Kuschyk J, Jones P, Duffy E, Husby M, Stein K, Lambiase PD

**Background:** The subcutaneous implantable cardioverter-defibrillator (S-ICD) was developed to defibrillate ventricular arrhythmias, avoiding drawbacks of transvenous leads. The global EFFORTLESS S-ICD (Evaluation oF FactORs ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD) registry is collecting outcomes in 985 patients during a 5-year follow-up. **Objectives:** The primary goal of the EFFORTLESS registry is to determine the safety of the S-ICD by evaluating complications and inappropriate shock rate.
**Methods:** This is the first report on the full patient cohort and study endpoints with follow-up >/=1 year. The predefined endpoints are 30- and 360-day complications, and shocks for atrial fibrillation or supraventricular tachycardia.
**Results:** Patients were followed for 3.1 +/- 1.5 years and 82 completed the study protocol 5-year visit. Average age was 48 years, 28% were women, ejection fraction was 43 +/- 18%, and 65% had a primary prevention indication. The S-ICD system and procedure complication rate was 4.1% at 30 days and 8.4% at 360 days. The 1-year complication rate trended toward improvement from the first to last quartile of

enrollment (11.3% [quartile 1]) to 7.8% [quartile 2], 6.6% [quartile 3], and 7.4% [quartile 4]; quartile 1 vs. quartiles 2 to 4; p = 0.06). Few device extractions occurred due to need for antitachycardia (n = 5), or biventricular (n = 4) or bradycardia pacing (n = 1). Inappropriate shocks occurred in 8.1% at 1 year and 11.7% after 3.1 years. At implant, 99.5% of patients had a successful conversion of induced ventricular tachycardia or ventricular fibrillation. The 1- and 5-year rates of appropriate shock were 5.8% and 13.5%, respectively. Conversion success for discrete spontaneous episodes was 97.4% overall.
**Conclusions:** This registry demonstrates that the S-ICD fulfills predefined endpoints for safety and efficacy. Midterm performance rates on complications, inappropriate shocks, and conversion efficacy were comparable to rates observed in transvenous implantable cardioverter-defibrillator studies. (Evaluation oF Factors ImpacTing CLinical Outcome and Cost EffectiveneSS of the S-ICD [The EFFORTLESS S-ICD Registry]; NCT01085435).

Gepubliceerd in: J Am Coll Cardiol 2017 Aug 15;70(7):830-41
Impact factor: 19.896

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Totale impact factor: 180.496
Gemiddelde impact factor: 5.822

Aantal artikelen 1e, 2e of laatste auteur: 14
Totale impact factor: 63.754
Gemiddelde impact factor: 4.554

# Gynaecologie

**1. Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term**

Cluver C, Novikova N, Koopmans CM, West HM

**Background:** Hypertensive disorders in pregnancy are significant contributors to maternal and perinatal morbidity and mortality. These disorders include well-controlled chronic hypertension, gestational hypertension (pregnancy-induced hypertension) and mild pre-eclampsia. The definitive treatment for these disorders is planned early delivery and the alternative is to manage the pregnancy expectantly if severe uncontrolled hypertension is not present, with close maternal and fetal monitoring. There are benefits and risks associated with both, so it is important to establish the safest option. OBJECTIVES: To assess the benefits and risks of a policy of planned early delivery versus a policy of expectant management in pregnant women with hypertensive disorders, at or near term (from 34 weeks onwards). SEARCH

**Methods:** We searched Cochrane Pregnancy and Childbirth Trials Register (12 January 2016) and reference lists of retrieved studies. SELECTION CRITERIA: Randomised trials of a policy of planned early delivery (by induction of labour or by caesarean section) compared with a policy of delayed delivery ("expectant management") for women with hypertensive disorders from 34 weeks' gestation. Cluster-randomised trials would have been eligible for inclusion in this review, but we found none.Studies using a quasi-randomised design are not eligible for inclusion in this review. Similarly, studies using a cross-over design are not eligible for inclusion, because they are not a suitable study design for investigating hypertensive disorders in pregnancy. DATA COLLECTION AND ANALYSIS: Two review authors independently assessed eligibility and risks of bias. Two review authors independently extracted data. Data were checked for accuracy. MAIN

**Results:** We included five studies (involving 1819 women) in this review.There was a lower risk of composite maternal mortality and severe morbidity for women randomised to receive planned early delivery (risk ratio (RR) 0.69, 95% confidence interval (CI) 0.57 to 0.83, two studies, 1459 women (evidence graded high)). There were no clear differences between subgroups based on our subgroup analysis by gestational age, gestational week or condition. Planned early delivery was associated with lower risk of HELLP syndrome (RR 0.40, 95% CI 0.17 to 0.93, 1628 women; three studies) and severe renal impairment (RR 0.36, 95% CI 0.14 to 0.92, 100 women, one study).There was not enough information to draw any conclusions about the effects on composite infant mortality and severe morbidity. We observed a high level of heterogeneity between the two studies in this analysis (two studies, 1459 infants, I2 = 87%, Tau2 = 0.98), so we did not pool data in meta-analysis. There were no clear differences between subgroups based on our subgroup analysis by

gestational age, gestational week or condition. Planned early delivery was associated with higher levels of respiratory distress syndrome (RR 2.24, 95% CI 1.20 to 4.18, three studies, 1511 infants), and NICU admission (RR 1.65, 95% CI 1.13 to 2.40, four studies, 1585 infants).There was no clear difference between groups for caesarean section (RR 0.91, 95% CI 0.78 to 1.07, 1728 women, four studies, evidence graded moderate), or in the duration of hospital stay for the mother after delivery of the baby (mean difference (MD) -0.16 days, 95% CI -0.46 to 0.15, two studies, 925 women, evidence graded moderate) or for the baby (MD -0.20 days, 95% CI -0.57 to 0.17, one study, 756 infants, evidence graded moderate).Two fairly large, well-designed trials with overall low risk of bias contributed the majority of the evidence. Other studies were at low or unclear risk of bias. No studies attempted to blind participants or clinicians to group allocation, potentially introducing bias as women and staff would have been aware of the intervention and this may have affected aspects of care and decision-making.The level of evidence was graded high (composite maternal mortality and morbidity), moderate (caesarean section, duration of hospital stay after delivery for mother, and duration of hospital stay after delivery for baby) or low (composite infant mortality and morbidity). Where the evidence was downgraded, it was mostly because the confidence intervals were wide, crossing both the line of no effect and appreciable benefit or harm. AUTHORS'
**Conclusions:** For women suffering from hypertensive disorders of pregnancy after 34 weeks, planned early delivery is associated with less composite maternal morbidity and mortality. There is no clear difference in the composite outcome of infant mortality and severe morbidity; however, this is based on limited data (from two trials) assessing all hypertensive disorders as one group.Further studies are needed to look at the different types of hypertensive diseases and the optimal timing of delivery for these conditions. These studies should also include infant and maternal morbidity and mortality outcomes, caesarean section, duration of hospital stay after delivery for mother and duration of hospital stay after delivery for baby.An individual patient meta-analysis on the data currently available would provide further information on the outcomes of the different types of hypertensive disease encountered in pregnancy

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Impact factor: 6.264

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**2. Surgery for patients with newly diagnosed advanced ovarian cancer: which patient, when and extent?**
Eggink FA, Koopmans CM, Nijman HW

**Purpose of review:** Cytoreduction to no residual disease is the mainstay of primary treatment for advanced epithelial ovarian cancer (AdvEOC). This review addresses recent insights on optimal patient selection, timing, and extent of surgery, intended to optimize cytoreduction in patients with AdvEOC.
**Recent findings:** Clinical guidelines recommend primary cytoreductive surgery (PCS) for AdvEOC patients with a high likelihood of achieving complete cytoreduction with acceptable morbidity. In line with this, preoperative prediction markers such as cancer antigen-125, histologic and genomic factors, innovative imaging modalities, and the performance of a diagnostic laparoscopy have been suggested to improve clinical decision-making with regard to optimal timing of cytoreductive surgery. To determine whether these strategies should be incorporated into clinical practice validation in randomized clinical trials is essential.
**Summary:** The past decade has seen a paradigm shift in the number of AvdEOC patients that are being treated with upfront neoadjuvant chemotherapy instead of PCS. However, although neoadjuvant chemotherapy may reduce morbidity at the time of interval cytoreductive surgery, no favorable impact on survival has been demonstrated and it may induce resistance to chemotherapy. Therefore, optimizing patient selection for PCS is crucial. Furthermore, surgical innovations in patients diagnosed with AvdEOC should focus on improving survival outcomes

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Impact factor: 3.414

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**3. Authors' reply re: 'Word catheter and marsupialisation in women with a cyst or abscess of the** Bartholin gland (WoMan-trial): a randomised clinical trial'
Kroese A, Van der Velde M, Morssink L, Zafarmand H, Mol B, Reesink-Peters N

Gepubliceerd: BJOG 2017 Mar;124(4):696-7
Impact factor: 5.051

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**4. Word catheter and marsupialisation in women with a cyst or abscess of the Bartholin gland (WoMan-trial): a randomised clinical trial**
Kroese JA, Van der Velde M, Morssink LP, Zafarmand MH, Geomini P, van Kesteren P, Radder CM, van der Voet LF, Roovers J, Graziosi G, van Baal WM, van Bavel J, Catshoek R, Klinkert ER, Huirne J, Clark TJ, Mol B, Reesink-Peters N

**Objective:** To compare recurrence of a cyst or abscess of the Bartholin gland after surgical treatment using a Word catheter or marsupialisation.
**Design:** Multicentre, open-label, randomised controlled trial.

**Setting:** Eighteen hospitals in the Netherlands and one hospital in England.
**Population:** Women with a symptomatic cyst or abscess of the Bartholin gland.
**Methods:** Women were randomised to treatment with Word catheter or marsupialisation.
**Main outcome measures**: The primary outcome was recurrence of the cyst or abscess within 1 year of treatment. The secondary outcomes included pain during and after treatment (measured on a 10-point scale), use of analgesics, and time from diagnosis to treatment. Analysis was by intention-to-treat. To assess whether marsupialisation would reduce the recurrence rate by 5% (from 20 to 15%) we needed to include 160 women (alpha error 0.05, beta error 0.2).
**Results:** One hundred and sixty-one women were randomly allocated to treatment by Word catheter (n = 82) or marsupialisation (n = 79) between August 2010 and May 2014. Baseline characteristics were comparable. Recurrence occurred in 10 women (12%) allocated to Word catheter versus eight women (10%) allocated to marsupialisation: relative risk (RR) 1.1, 95% confidence interval (CI) 0.64-1.91; P = 0.70. Pain scores after treatment were also comparable. In the first 24 hours after treatment, 33% used analgesics in the Word catheter group versus 74% in the marsupialisation group (P < 0.001). Time from diagnosis to treatment was 1 hour for placement of Word catheter versus 4 hours for marsupialisation (P = 0.001).
**Conclusions:** In women with an abscess or cyst of the Bartholin gland, treatment with Word catheter and marsupialisation results in comparable recurrence rates.
**Tweetable abstract**: Comparable recurrence rates for treatment of Bartholinic abscess/cyst with Word catheter and marsupialisation

Gepubliceerd: BJOG 2017;124(2):243-9
Impact factor: 5.051

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**5. Laparoscopy to Predict the Result of Primary Cytoreductive Surgery in Patients With Advanced Ovarian Cancer: A Randomized Controlled Trial**
Rutten MJ, van Meurs HS, van de Vrie R, Gaarenstroom KN, Naaktgeboren CA, van Gorp T, Ter Brugge HG, Hofhuis W, Schreuder HW, Arts HJ, Zusterzeel PL, Pijnenborg JM, van Haaften M, Fons G, Engelen MJ, Boss EA, Vos MC, Gerestein KG, Schutter EM, Opmeer BC, Spijkerboer AM, Bossuyt PM, Mol BW, Kenter GG, Buist MR

**Purpose:** To investigate whether initial diagnostic laparoscopy can prevent futile primary cytoreductive surgery (PCS) by identifying patients with advanced-stage ovarian cancer in whom > 1 cm of residual disease will be left after PCS.
**Patients and Methods:** This multicenter, randomized controlled trial was undertaken within eight gynecologic cancer centers in the Netherlands. Patients with suspected

advanced-stage ovarian cancer who qualified for PCS were eligible. Participating patients were randomly assigned to either laparoscopy or PCS. Laparoscopy was used to guide selection of primary treatment: either primary surgery or neoadjuvant chemotherapy followed by interval surgery. The primary outcome was futile laparotomy, defined as a PCS with residual disease of > 1 cm. Primary analyses were performed according to the intention-to-treat principle.
**Results:** Between May 2011 and February 2015, 201 participants were included, of whom 102 were assigned to diagnostic laparoscopy and 99 to primary surgery. In the laparoscopy group, 63 (62%) of 102 patients underwent PCS versus 93 (94%) of 99 patients in the primary surgery group. Futile laparotomy occurred in 10 (10%) of 102 patients in the laparoscopy group versus 39 (39%) of 99 patients in the primary surgery group (relative risk, 0.25; 95% CI, 0.13 to 0.47; P < .001). In the laparoscopy group, three (3%) of 102 patients underwent both primary and interval surgery compared with 28 (28%) of 99 patients in the primary surgery group ( P < .001).
**Conclusion:** Diagnostic laparoscopy reduced the number of futile laparotomies in patients with suspected advanced-stage ovarian cancer. In women with a plan for PCS, these data suggest that performance of diagnostic laparoscopy first is reasonable and that if cytoreduction to < 1 cm of residual disease seems feasible, to proceed with PCS

Gepubliceerd: J Clin Oncol 2017 Feb 20;35(6):613-21
Impact factor: 24.008

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**6. Clinical inference of maternal renal venous Doppler ultrasonography**
Staelens AS, Vonck S, Tomsin K, Gyselaers W

Gepubliceerd: Ultrasound Obstet Gynecol 2017 Jan;49(1):155-6
Impact factor: 4.710

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**7. An economic analysis of immediate delivery and expectant monitoring in women with hypertensive disorders of pregnancy, between 34 and 37 weeks of gestation (HYPITAT-II)**
van Baaren GJ, Broekhuijsen K, van Pampus MG, Ganzevoort W, Sikkema JM, Woiski MD, Oudijk MA, Bloemenkamp K, Scheepers H, Bremer HA, Rijnders R, van Loon AJ, Perquin D, Sporken J, Papatsonis D, van Huizen ME, Vredevoogd CB, Brons J, Kaplan M, van Kaam AH, Groen H, Porath M, van den Berg PP, Mol B, Franssen M, Langenveld J

**Objective:** To assess the economic consequences of immediate delivery compared with expectant monitoring in women with preterm non-severe hypertensive disorders of pregnancy.
**Design:** A cost-effectiveness analysis alongside a randomised controlled trial (HYPITAT-II).
**Setting:** Obstetric departments of seven academic hospitals and 44 non-academic hospitals in the Netherlands.
**Population:** Women diagnosed with non-severe hypertensive disorders of pregnancy between 340/7 and 370/7 weeks of gestation, randomly allocated to either immediate delivery or expectant monitoring.
**Methods:** A trial-based cost-effectiveness analysis was performed from a healthcare perspective until final maternal and neonatal discharge. MAIN OUTCOME MEASURES: Health outcomes were expressed as the prevalence of respiratory distress syndrome, defined as the need for supplemental oxygen for >24 hours combined with radiographic findings typical for respiratory distress syndrome. Costs were estimated from a healthcare perspective until maternal and neonatal discharge.
**Results:** The average costs of immediate delivery (n = 352) were euro10 245 versus euro9563 for expectant monitoring (n = 351), with an average difference of euro682 (95% confidence interval, 95% CI -euro618 to euro2126). This 7% difference predominantly originated from the neonatal admissions, which were euro5672 in the immediate delivery arm and euro3929 in the expectant monitoring arm.
**Conclusion:** In women with mild hypertensive disorders between 340/7 and 370/7 weeks of gestation, immediate delivery is more costly than expectant monitoring as a result of differences in neonatal admissions. These findings support expectant monitoring, as the clinical outcomes of the trial demonstrated that expectant monitoring reduced respiratory distress syndrome for a slightly increased risk of maternal complications. TWEETABLE ABSTRACT: Expectant management in preterm hypertensive disorders is less costly compared with immediate delivery

Gepubliceerd: BJOG 2017 Feb;124(3):453-61
Impact factor: 5.051

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**8. Cost-effectiveness of laparoscopy as diagnostic tool before primary cytoreductive surgery in ovarian cancer**
van de Vrie R, van Meurs HS, Rutten MJ, Naaktgeboren CA, Opmeer BC, Gaarenstroom KN, van Gorp T, Ter Brugge HG, Hofhuis W, Schreuder HWR, Arts HJG, Zusterzeel PLM, Pijnenborg JMA, van Haaften M, Engelen MJA, Boss EA, Vos MC, Gerestein KG, Schutter EMJ, Kenter GG, Bossuyt PMM, Mol BW, Buist MR

**Objective:** To evaluate the cost-effectiveness of a diagnostic laparoscopy prior to primary cytoreductive surgery to prevent futile primary cytoreductive surgery (i.e. leaving >1cm residual disease) in patients suspected of advanced stage ovarian cancer.
**Methods:** An economic analysis was conducted alongside a randomized controlled trial in which patients suspected of advanced stage ovarian cancer who qualified for primary cytoreductive surgery were randomized to either laparoscopy or primary cytoreductive surgery. Direct medical costs from a health care perspective over a 6-month time horizon were analyzed. Health outcomes were expressed in quality-adjusted life-years (QALYs) and utility was based on patient's response to the EQ-5D questionnaires. We primarily focused on direct medical costs based on Dutch standard prices.
**Results:** We studied 201 patients, of whom 102 were randomized to laparoscopy and 99 to primary cytoreductive surgery. No significant difference in QALYs (utility=0.01; 95% CI 0.006 to 0.02) was observed. Laparoscopy reduced the number of futile laparotomies from 39% to 10%, while its costs were euro 1400 per intervention, making the overall costs of both strategies comparable (difference euro -80 per patient (95% CI -470 to 300)). Findings were consistent across various sensitivity analyses.
**Conclusion:** In patients with suspected advanced stage ovarian cancer, a diagnostic laparoscopy reduced the number of futile laparotomies, without increasing total direct medical health care costs, or adversely affecting complications or quality of life

Gepubliceerd: Gynecol Oncol 2017 Jun 20;146(3):449-56
Impact factor: 4.959

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**9. Blood pressure patterns in women with gestational hypertension or mild preeclampsia at term**
van der Tuuk K, Tajik P, Koopmans CM, van den Berg PP, Mol BWJ, van Pampus MG, Groen H

**Objective:** Gestational hypertension (GH) and mild preeclampsia (PE) represent the most common medical complications of pregnancy, with the majority of cases developing at or near term. There is little knowledge of the course of blood pressure over time in these women. We explored the pattern of systolic and diastolic blood pressure over time in women with GH or mild PE at term participating in the HYPITAT trial, and we attempted to identify clinical factors influencing these blood pressure patterns and the impact of severe hypertension on clinical management.
**Study design:** We used data from the HYPITAT trial, that included women with a singleton pregnancy with a fetus in cephalic position between 36 and 41 weeks of

gestation with the diagnosis of GH or mild PE. Blood pressure measurements were performed from randomization or admission until delivery or discharge from the hospital. We included the highest blood pressure of each day. We evaluated systolic and diastolic blood pressure change over time, as well as the influence of clinical characteristics and laboratory findings on the course of blood pressure. We used univariate and multivariate regression analysis with a backward stepwise algorithm for the selection of variables. The model with the best fit (lowest AIC) was selected as the final model. We also compared mode of delivery for women with and without severe hypertension.
**Results:** We studied 1076 women who had 4188 blood pressure measurements done. The systolic blood pressure showed a significant non-linear increase over time and for the diastolic blood pressure the pattern was also non-linear. In the multivariable model of systolic blood pressure change over time, nulliparity, ethnicity, systolic blood pressure (at baseline), BMI and LDH at randomization influenced the course of blood pressure. In the diastolic blood pressure model ALT and the baseline diastolic blood pressure had a significant influence. When we explored the association between blood pressure and mode of delivery, it appeared that development of severe hypertension was a risk factor for Caesarean section.
**Conclusion:** The blood pressure in patients with GH or PE at term showed a non-linear increase with time, which was aggravated by clinical characteristics. Development of severe hypertension was a risk factor for Caesarean section, which may explain the elevated Caesarean section rates in the expectant monitoring group in the HYPITAT trial

Gepubliceerd: Eur J Obstet Gynecol Reprod Biol 2017 Mar;210:360-5
Impact factor: 1.666

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**10. Diagnostic workup for postmenopausal bleeding: a randomised controlled trial**
van Hanegem N, Breijer MC, Slockers SA, Zafarmand MH, Geomini P, Catshoek R, Pijnenborg J, van der Voet LF, Dijkhuizen F, van Hoecke G, Reesink-Peters N, Veersema S, van Hooff M, van Kesteren P, Huirne JA, Opmeer BC, Bongers MY, Mol B, Timmermans A

**Objective:** To evaluate the effectiveness of hysteroscopy for the detection and treatment of endometrial polyps versus expectant management in women with postmenopausal bleeding (PMB), a thickened endometrium and benign endometrial sampling.
**Design:** Multicentre, randomised controlled trial.

**Setting:** Three academic hospitals and nine non-academic teaching hospitals in the Netherlands.
**Population:** Women with PMB, an endometrial thickness >4 mm and benign result from endometrial sampling.
**Methods:** Women were randomised to either further diagnostic workup by hysteroscopy (preceded by saline infusion sonography) or expectant management.
**Main outcomes:** The primary outcome measure was recurrence of PMB within a year after randomisation. Secondary outcome measures were time to recurrent bleeding and recurrent bleeding after more than 1 year. In the hysteroscopy group, the presence of polyps and the results of their histology were registered.
**Results:** Between January 2010 and October 2013, 200 women were randomised; 98 to hysteroscopy and 102 to expectant management. Within 1 year a total of 15 women (15.3%) in the hysteroscopy group experienced recurrent bleeding, versus 18 (18.0%) in the expectant management group (relative risk 0.85 (95% CI 0.46-1.59). In the hysteroscopy group, 50/98 (51%) polyps were diagnosed of which 6/98 (6%) showed evidence of endometrial (pre)malignancy; final pathology results after hysterectomy showed three women with hyperplasia with atypia and three women with endometrial cancer.
**Conclusion:** In women with PMB, a thickened endometrium and benign endometrial sampling, operative hysteroscopy does not reduce recurrent bleeding. Hysteroscopy detected focal endometrial (pre)malignancy in 6% of women who had benign endometrial sampling. This finding indicates that in these women, further diagnostic workup is warranted to detect focal (pre)malignancies, missed by blind endometrial sampling.
**Tweetable abstract:** In women with PMB, hysteroscopy does not reduce recurrent bleeding but is warranted to detect focal malignancy

Gepubliceerd: BJOG 2017 Jan;124(2):231-40
Impact factor: 5.051

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**11. Pessary or Progesterone to Prevent Preterm delivery in women with short cervical length: the Quadruple P randomised controlled trial**
van Zijl MD, Koullali B, Naaktgeboren CA, Schuit E, Bekedam DJ, Moll E, Oudijk MA, van Baal WM, de Boer MA, Visser H, van Drongelen J, van de Made FW, Vollebregt KC, Muller MA, Bekker MN, Brons JTJ, Sueters M, Langenveld J, Franssen MT, Schuitemaker NW, van BE, Scheepers HCJ, de Boer K, Tepe EM, Huisjes AJM, Hooker AB, Verheijen ECJ, Papatsonis DN, Mol BWJ, Kazemier BM, Pajkrt E

**Background:** Preterm birth is in quantity and in severity the most important topic in obstetric care in the developed world. Progestogens and cervical pessaries have

been studied as potential preventive treatments with conflicting results. So far, no study has compared both treatments. METHODS/
**Design:** The Quadruple P study aims to compare the efficacy of vaginal progesterone and cervical pessary in the prevention of adverse perinatal outcome associated with preterm birth in asymptomatic women with a short cervix, in singleton and multiple pregnancies separately. It is a nationwide open-label multicentre randomized clinical trial (RCT) with a superiority design and will be accompanied by an economic analysis. Pregnant women undergoing the routine anomaly scan will be offered cervical length measurement between 18 and 22 weeks in a singleton and at 16-22 weeks in a multiple pregnancy. Women with a short cervix, defined as less than, or equal to 35 mm in a singleton and less than 38 mm in a multiple pregnancy, will be invited to participate in the study. Eligible women will be randomly allocated to receive either progesterone or a cervical pessary. Following randomization, the silicone cervical pessary will be placed during vaginal examination or 200 mg progesterone capsules will be daily self-administered vaginally. Both interventions will be continued until 36 weeks gestation or until delivery, whichever comes first. Primary outcome will be composite adverse perinatal outcome of perinatal mortality and perinatal morbidity including bronchopulmonary dysplasia, intraventricular haemorrhage grade III and IV, periventricular leukomalacia higher than grade I, necrotizing enterocolitis higher than stage I, Retinopathy of prematurity (ROP) or culture proven sepsis. These outcomes will be measured up until 10 weeks after the expected due date. Secondary outcomes will be, among others, time to delivery, preterm birth rate before 28, 32, 34 and 37 weeks, admission to neonatal intensive care unit, maternal morbidity, maternal admission days for threatened preterm labour and costs.
**Discussion:** This trial will provide evidence on whether vaginal progesterone or a cervical pessary is more effective in decreasing adverse perinatal outcome in both singletons and multiples.
**Trial registration:** Trial registration number: NTR 4414 . Date of registration January 29th 2014

Gepubliceerd: BMC Pregnancy Childbirth 2017 Sep 4;17(1):284
Impact factor: 2.263

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**12. The effect of elevated progesterone levels before HCG triggering in modified natural cycle frozen-thawed embryo transfer cycles.**
Groenewoud ER, Macklon NS, Cohlen BJ; ANTARCTICA Study Group (Includes Hoozemans DA)

Recent studies suggest that elevated late follicular phase progesterone concentrations after ovarian stimulation for IVF may result in embryo-endometrial

asynchrony, reducing the chance of successful implantation after fresh embryo transfer. It remains unclear to what extent elevated late follicular phase progesterone levels may occur in unstimulated cycles before frozen-thawed embryo transfer, or what affect they may have on outcomes. In this cohort study, 271 patients randomized to the modified natural cycle arm of a randomized controlled trial comparing two endometrial preparation regimens underwent late follicular phase progesterone and LH testing. A receiver operating characteristic curve was constructed to identify a progesterone cut-off level with the best predictive value for live birth (progesterone level ≥4.6 nmol/l). A total of 24.4% of patients revealed an isolated elevated serum progesterone of 4.6 nmol/l or greater, and 44.3% showed an elevated progesterone level in association with a rise in LH. Neither endocrine disruption affected outcomes, with live birth rates of 12.9% versus 10.6% (OR 0.6, 95% CI 0.19 to 1.9) and 11.9% versus 17.5% (OR 1.6, 95% CI 0.79 to 3.1), respectively. Whether monitoring of progesterone and LH in natural cycle frozen-thawed embryo transfer has added clinical value should be studied further.

Gepubliceerd: Reprod Biomed Online. 2017 May;34(5):546-554
Impact factor: 3.249

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**13. The SUPER study: protocol for a randomised controlled trial comparing follicle-stimulating hormone and clomiphene citrate for ovarian stimulation in intrauterine insemination**

Danhof NA, van WM, Koks CAM, Gianotten J, de Bruin JP, Cohlen BJ, van der Ham DP, Klijn NF, van Hooff MHA, Broekmans FJM, Fleischer K, Janssen CAH, Rijn van Weert JM, van Disseldorp J, Twisk M, Traas M, Verberg MFG, Pelinck MJ, Visser J, Perquin DAM, Boks DES, Verhoeve HR, van Heteren CF, Mol BWJ, Repping S, van der Veen F, Mochtar MH

**Objective:** To study the effectiveness of four cycles of intrauterine insemination (IUI) with ovarian stimulation (OS) by follicle-stimulating hormone (FSH) or by clomiphene citrate (CC), and adherence to strict cancellation criteria.
**Setting:** Randomised controlled trial among 22 secondary and tertiary fertility clinics in the Netherlands.
**Participants:** 732 women from couples diagnosed with unexplained or mild male subfertility and an unfavourable prognosis according to the model of Hunault of natural conception.
**Interventions:** Four cycles of IUI-OS within a time horizon of 6 months comparing FSH 75 IU with CC 100 mg. The primary outcome is ongoing pregnancy conceived within 6 months after randomisation, defined as a positive heartbeat at 12 weeks of gestation. Secondary outcomes are cancellation rates, number of cycles with a

monofollicular or with multifollicular growth, number of follicles >14 mm at the time of ovulation triggering, time to ongoing pregnancy, clinical pregnancy, miscarriage, live birth and multiple pregnancy. We will also assess if biomarkers such as female age, body mass index, smoking status, antral follicle count and endometrial aspect and thickness can be used as treatment selection markers.
**Ethics and dissemination:** The study has been approved by the Medical Ethical Committee of the Academic Medical Centre and from the Dutch Central Committee on Research involving Human Subjects (CCMO NL 43131-018-13). Results will be disseminated through peer-reviewed publications and presentations at international scientific meetings.
**Trial registration number:** NTR4057.

BMJ Open 2017 May 25;7(5):e015680
Impact factor: 2.369

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Totale impact factor: 73.106
Gemiddelde impact factor: 5.624

Aantal artikelen 1e, 2e of laatste auteur: 4
Totale impact factor: 18.226
Gemiddelde impact factor: 4.557

# Heelkunde

**1. Editor's Choice - Management of the Diseases of Mesenteric Arteries and Veins: Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS)**
Bjorck M, Koelemay M, Acosta S, Bastos Goncalves F, Kolbel T, Kolkman JJ, Lees T, Lefevre JH, Menyhei G, Oderich G, Kolh P, de Borst GJ, Chakfe N, Debus S, Hinchliffe R, Kakkos S, Koncar I, Sanddal Lindholt J, Vega de Ceniga M, Vermassen F, Verzini F, Geelkerken B, Gloviczki P, Huber T, Naylor R

Gepubliceerd: Eur J Vasc Endovasc Surg 2017 Apr;53(4):460-510
Impact factor: 4.061

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**2. Chronic Mesenteric Ischemia: when and how to intervene on patients with celiac/SMA stenosis**
Blauw J, Bulut T, Eenhoorn P, Beuk RJ, Brusse-Keizer M, Kolkman J, Geelkerken RH

Studies that compared open surgical mesenteric artery repair (OSMAR) with percutaneous mesenteric artery stenting (PMAS) in patients with chronic mesenteric ischemia (CMI) are based on merely older studies in which only a minority of patients received PMAS. This does not reflect the current PMAS-first choice treatment paradigm. This article focused on the present opinions and changes in outcomes of OSMAR for CMI in the era of preferred use of PMAS. Patients who received OSMAR for CMI from 1997 until 2014 in a tertiary referral centre for chronic mesenteric ischemia were included in this report. Patients were divided into two groups, the historical OSMAR preferred group and present PMAS preferred group. Patient characteristics, SVS comorbidity severity score, clinical presentation and number of diseased mesenteric arteries were not significantly changed after the widespread introduction of PMAS. In the present PMAS first era there were trends of less open surgical mesenteric artery multi-vessel repair, less antegrade situated bypasses, decreased clinical success but improved survival after OSMAR. Elective OSMAR should only be used in patients with substantial physiologic reserve and who have unfavourable mesenteric lesions, failed PMAS or multiple recurrences of in-stent stenosis/occlusion. PMAS in CMI patients is evolved from 'bridge to surgery' to nowadays first choice treatment and "bridge to repeated PMAS" in almost all patients with CMI.

Gepubliceerd: J Cardiovasc Surg (Torino) 2017;58(2):321-8
Impact factor: 1.632

**3. Mesenteric vascular treatment 2016: from open surgical repair to endovascular revascularization**
Blauw JT, Bulut T, Oderich GS, Geelkerken BR

The rise of endovascular techniques has improved the outcome of mesenteric ischemia. Key principle in reduction of morbidity and mortality is "revascularization first, resection later". We believe that mesenteric ischemia is a clinical challenge demanding 24/7 multidisciplinary team availability. This article describes the current insights into treatment of mesenteric ischemia.

Gepubliceerd: Best Pract Res Clin Gastroenterol 2017 Feb;31(1):75-84
Impact factor: 3.762

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**4. An evaluation of the validity of the pre-operative oxygen uptake efficiency slope as an indicator of cardiorespiratory fitness in elderly patients scheduled for major colorectal surgery**
Bongers BC, Berkel AE, Klaase JM, van Meeteren NL

This study aimed to investigate the validity of the oxygen uptake efficiency slope as an objective and submaximal indicator of cardiorespiratory fitness in elderly patients scheduled for major colorectal surgery. Patients >/= 60 years of age, with a metabolic equivalent score using the Veterans Activity Questionnaire </= 7 and scheduled for major colorectal surgery participated in a pre-operative cardiopulmonary exercise test. The oxygen uptake efficiency slope was calculated up to different exercise intensities, using 100%, 90% and 80% of the exercise data. Data from 71 patients (47 men, mean (SD) age 75.2 (6.7) years) were analysed. The efficiency slope obtained from all the data was statistically significantly different from the values when 90% ($p = 0.027$) and 80% ($p = 0.023$) of the data were used. The 90% and 80% values did not differ significantly from each other ($p = 0.152$). Correlations between the oxygen uptake efficiency slope and the peak oxygen uptake ranged from 0.816 to 0.825 (all $p < 0.001$), and correlations between oxygen uptake efficiency slope and the ventilatory anaerobic threshold ranged from 0.793 to 0.805 (all $p < 0.001$). Receiver operating characteristic curves showed that the oxygen uptake efficiency slope is a sensitive and specific predictor of a peak oxygen uptake </= 18.2 ml.kg-1 .min-1 , with an area under the curve (95%CI) of 0.876 (0.780-0.972, $p < 0.001$) and a ventilatory anaerobic threshold </= 11.1 ml.kg-1 .min-1 , with an area under the curve (95%CI) of 0.828 (0.726-0.929, $p < 0.001$). These correlations suggest that the oxygen uptake efficiency slope provides a valid (sub)maximal measure of cardiorespiratory fitness in

these patients, and the predictive ability described indicates that it might help discriminate patients at higher risk of postoperative morbidity. However, future research should investigate the prognostic value of the oxygen uptake efficiency slope for postoperative outcomes.

Gepubliceerd: Anaesthesia 2017 Jul 25;72(10):1206-16
Impact factor: 4.741

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**5. Is our treatment of well-differentiated thyroid cancer too aggressive? Hemithyroidectomy versus total thyroidectomy**
Bongers PJ, Kluijfhout WP, Vriens MW, Mastboom WJ, Lutke Holzik MF

Recent literature shows that hemithyroidectomy is a safe alternative for total thyroidectomy in the treatment of patients with well-differentiated thyroid cancer up to 4 cm in diameter and a low risk of recurrence. According to criteria of the 2015 American Thyroid Association guidelines, more than 28% of patients with well-differentiated thyroid cancer of a Dutch cohort would be eligible for hemithyroidectomy instead of the total thyroidectomy they actually underwent. However, standardisation and high quality pre- and postoperative diagnostics are required for responsible implementation of this new guideline in Dutch healthcare.

Gepubliceerd: Ned Tijdschr Geneeskd 2017;161:D1852
Impact factor: 0

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**6. Prophylactic Mesh Placement During Formation of an End-colostomy Reduces the Rate of Parastomal Hernia: Short-term Results of the Dutch PREVENT-trial**
Brandsma HT, Hansson BM, Aufenacker TJ, van Geldere D, Lammeren FM, Mahabier C, Makai P, Steenvoorde P, de Vries Reilingh TS, Wiezer MJ, de Wilt JH, Bleichrodt RP, Rosman C, Dutch Prevent Study group

**Objective:** The aim of this study was to investigate the incidence of parastomal hernias (PSHs) after end-colostomy formation using a polypropylene mesh in a randomized controlled trial versus conventional colostomy formation.
**Background:** A PSH is the most frequent complication after stoma formation. Symptoms may range from mild abdominal pain to life-threatening obstruction and strangulation. The treatment of a PSH is notoriously difficult and recurrences up to 20% have been reported despite the use of mesh. This has moved surgical focus toward prevention.

**Methods:** Augmentation of the abdominal wall with a retro-muscular lightweight polypropylene mesh was compared with the traditional formation of a colostomy. In total, 150 patients (1:1 ratio) were included. The incidence of a PSH, morbidity, mortality, quality of life, and cost-effectiveness was measured after 1 year of follow-up.
**Results:** There was no difference between groups regarding demographics and predisposing factors for PSH. Three out of 67 patients (4.5%) in the mesh group and 16 out of 66 patients (24.2%) in the nonmesh group developed a PSH (P = 0.0011). No statistically significant difference was found in infections, concomitant hernias, SF-36 questionnaire, Von Korff pain score, and cost-effectiveness between both study groups.
**Conclusion:** Prophylactic augmentation of the abdominal wall with a retromuscular lightweight polypropylene mesh at the ostomy site significantly reduces the incidence of PSH without a significant difference in morbidity, mortality, quality of life, or cost-effectiveness.

Gepubliceerd: Ann Surg 2017 Apr;265(4):663-9
Impact factor: 8.980

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**7. Comparing the 2007 and 2011 GOLD Classifications as Predictors of all-Cause Mortality and Morbidity in COPD**
Brusse-Keizer M, Klatte M, Zuur-Telgen M, Koehorst-Ter Huurne K, van der Palen J, VanderValk P

To better classify patients with chronic obstructive pulmonary disease (COPD) for prognostic purposes and to tailor treatment, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 classification was revised in 2011. The primary aim of the current data analyses was to evaluate the accuracy of the GOLD 2007 and 2011 GOLD classifications to predict all-cause mortality and morbidity in a well-described COPD cohort. The prognostic values of both GOLD classifications, expressed as the C-statistic, were assessed in the Cohort of Mortality and Inflammation in COPD (COMIC) study of 795 COPD patients, with a follow-up of 3 years. Outcomes were all-cause mortality and morbidity. Morbidity was defined as time until first COPD-related hospitalisation and time until first community-acquired pneumonia (CAP). The prognostic value of the GOLD 2011 classification was compared between symptom classification based on the modified Medical Research Council (mMRC) score and the Clinical COPD Questionnaire (CCQ) scores with two different thresholds. Although the GOLD 2011 CCQ classification had the highest accuracy to predict mortality and morbidity in our study, the C-statistics differed only numerically. Furthermore, our study showed that the instrument used to determine

the level of symptoms in the GOLD 2011 classification has not only important consequences on the mortality prognosis, but also affects the morbidity prognosis in COPD. Therefore, patients' estimated prognosis could alter when different types of tools are used to evaluate the prognosis.

Gepubliceerd: COPD 2017 Feb;14(1):7-14
Impact factor: 2.576

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**8. Long-Term Results of Endovascular Treatment of Atherosclerotic Stenoses or Occlusions of the Coeliac and Superior Mesenteric Artery in Patients With Mesenteric Ischaemia**

Bulut T, Oosterhof-Berktas R, Geelkerken RH, Brusse-Keizer M, Stassen EJ, Kolkman JJ

**Introduction:** Over the past decade, primary percutaneous mesenteric artery stenting (PMAS) has become an alternative to open revascularisation for treatment of mesenteric ischaemia. Institutes have presented favourable short-term outcomes after PMAS, but there is a lack of data on long-term stent patency.
**Methods:** One hundred and forty-one patients treated by PMAS for acute and chronic mesenteric ischaemia over an 8 year period were studied. Anatomical success was assessed by duplex ultrasound and/or CT angiography. A stenosis >/=70% was considered to be a failure.
**Results:** Eighty-six coeliac arteries (CA) and 99 superior mesenteric arteries (SMA) were treated with PMAS in 141 patients. Nine CAs (10%) and 30 SMAs (30%) were occluded at the time of treatment. Median follow-up was 32 months (IQR 20-46). The overall primary patency rate at 12 and 60 months was 77.0% and 45.0%. The overall primary assisted patency rate was 90.3% and 69.8%. Overall secondary patency was 98.3% and 93.6%.
**Conclusion:** This study shows excellent long-term secondary patencies after PMAS, comparable with published data on long-term patencies after open surgical revascularisation.

Gepubliceerd: Eur J Vasc Endovasc Surg 2017 Feb 18;53(4):583-90
Impact factor: 4.061

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**9. Minimally invasive versus open distal pancreatectomy (LEOPARD): study protocol for a randomized controlled trial**

de Rooij T, van Hilst J, Vogel JA, van Santvoort HC, de Boer MT, Boerma D, van den Boezem PB, Bonsing BA, Bosscha K, Coene PP, Daams F, van Dam RM, Dijkgraaf

MG, van Eijck CH, Festen S, Gerhards MF, Groot KB, Hagendoorn J, van der Harst E, de Hingh IH, Dejong CH, Kazemier G, Klaase J, de Kleine RH, van Laarhoven CJ, Lips DJ, Luyer MD, Molenaar IQ, Nieuwenhuijs VB, Patijn GA, Roos D, Scheepers JJ, van der Schelling GP, Steenvoorde P, Swijnenburg RJ, Wijsman JH, Abu Hilal M, Busch OR, Besselink MG, Dutch Pancreatic Cancer Group

**Background:** Observational cohort studies have suggested that minimally invasive distal pancreatectomy (MIDP) is associated with better short-term outcomes compared with open distal pancreatectomy (ODP), such as less intraoperative blood loss, lower morbidity, shorter length of hospital stay, and reduced total costs. Confounding by indication has probably influenced these findings, given that case-matched studies failed to confirm the superiority of MIDP. This accentuates the need for multicenter randomized controlled trials, which are currently lacking. We hypothesize that time to functional recovery is shorter after MIDP compared with ODP even in an enhanced recovery setting.
**Methods:** LEOPARD is a randomized controlled, parallel-group, patient-blinded, multicenter, superiority trial in all 17 centers of the Dutch Pancreatic Cancer Group. A total of 102 patients with symptomatic benign, premalignant or malignant disease will be randomly allocated to undergo MIDP or ODP in an enhanced recovery setting. The primary outcome is time (days) to functional recovery, defined as all of the following: independently mobile at the preoperative level, sufficient pain control with oral medication alone, ability to maintain sufficient (i.e. >50%) daily required caloric intake, no intravenous fluid administration and no signs of infection. Secondary outcomes are operative and postoperative outcomes, including clinically relevant complications, mortality, quality of life and costs.
**Discussion:** The LEOPARD trial is designed to investigate whether MIDP reduces the time to functional recovery compared with ODP in an enhanced recovery setting.
**Trial registration**: Dutch Trial Register, NTR5188 . Registered on 9 April 2015.

Gepubliceerd: Trials 2017 Apr 8;18(1):166
Impact factor: 1.969

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**10. Diverging effects of diabetes mellitus in patients with peripheral artery disease and abdominal aortic aneurysm and the role of advanced glycation end-products: ARTERY study - protocol for a multicentre cross-sectional study**
de Vos LC, Boersema J, Hillebrands JL, Schalkwijk CG, Meerwaldt R, Breek JC, Smit AJ, Zeebregts CJ, Lefrandt JD

**Introduction:** Diabetes mellitus is a well-defined risk factor for peripheral artery disease (PAD), but protects against the development and growth of abdominal aortic

aneurysm (AAA). Diabetes mellitus is associated with arterial stiffening and peripheral arterial media sclerosis. Advanced glycation end-products (AGEs) are increased in diabetes mellitus and cardiovascular disease. AGEs are known to form cross-links between proteins and are associated with arterial stiffness. Whether AGEs contribute to the protective effects of diabetes mellitus in AAA is unknown. Therefore, the ARTERY (Advanced glycation end-pRoducts in patients with peripheral arTery disEase and abdominal aoRtic aneurYsm) study is designed to evaluate the role of AGEs in the diverging effects of diabetes mellitus on AAA and PAD.
**Methods and analysis:** This cross-sectional multicentre study will compare the amount, type and location of AGEs in the arterial wall in a total of 120 patients with AAA or PAD with and without diabetes mellitus (n=30 per subgroup). Also, local and systemic vascular parameters, including pulse wave velocity, will be measured to evaluate the association between arterial stiffness and AGEs. Finally, AGEs will be measured in serum, urine, and assessed in skin with skin autofluorescence using the AGE Reader.
**Ethics and dissemination:** This study is approved by the Medical Ethics committees of University Medical Center Groningen, Martini Hospital and Medisch Spectrum Twente, the Netherlands. Study results will be disseminated through peer-reviewed journals and scientific events.
**Trial registration number:** trialregister.nl NTR 5363.

Gepubliceerd: BMJ Open 2017 Apr 11;7(4):e012584
Impact factor: 2.369

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**11. In vivo geometry of the kissing stent and covered endovascular reconstruction of the aortic bifurcation configurations in aortoiliac occlusive disease**
Groot Jebbink E, Ter Mors TG, Slump CH, Geelkerken RH, Holewijn S, Reijnen MM

Objectives Various configurations of kissing stent (KS) configurations exist and patency rates vary. In response the covered endovascular reconstruction of the aortic bifurcation configuration was designed to minimize mismatch and improve outcome. The aim of the current study is to compare geometrical mismatch of kissing stent with the covered endovascular reconstruction of the aortic bifurcation configuration in vivo. Methods Post-operative computed tomographic data and patient demographics from 11 covered endovascular reconstruction of the aortic bifurcation and 11 matched kissing stent patients were included. A free hand region of interest and ellipse fitting method were applied to determine mismatch areas and volumes. Conformation of the stents to the vessel wall was expressed using the D-ratio. Results Patients were mostly treated for Rutherford category 2 and 3 (64%) with a lesion classification of

TASC C and D in 82%. Radial mismatch area and volume for the covered endovascular reconstruction of the aortic bifurcation group was significantly lower compared to the kissing stent configuration ( P < 0.05). The D-ratio did not significantly differ between groups. Measurements were performed with good intra-class correlation. There were no significant differences in the post-procedural aortoiliac anatomy. Conclusions The present study shows that radial mismatch exists in vivo and that large differences in mismatch exist, in favour of the covered endovascular reconstruction of the aortic bifurcation configuration. Future research should determine if the decreased radial mismatch results in improved local flow profiles and subsequent clinical outcome.

Gepubliceerd: Vascular 2017 Jan 1;25(6):635-41
Impact factor: 0.733

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**12. Meta-Analysis of Genome-Wide Association Studies for Abdominal Aortic Aneurysm Identifies Four New Disease-Specific Risk Loci**

Jones GT, Tromp G, Kuivaniemi H, Gretarsdottir S, Baas AF, Giusti B, Strauss E, van 't Hof FN, Webb T, Erdman R, Ritchie MD, Elmore JR, Verma A, Pendergrass S, Kullo IJ, Ye Z, Peissig PL, Gottesman O, Verma SS, Malinowski J, Rasmussen-Torvik LJ, Borthwick K, Smelser DT, Crosslin DR, de Andrade M, Ryer EJ, McCarty CA, Bottinger EP, Pacheco JA, Crawford DC, Carrell DS, Gerhard GS, Franklin DP, Carey DJ, Phillips VL, Williams MJ, Wei W, Blair R, Hill AA, Vasudevan TM, Lewis DR, Thomson IA, Krysa J, Hill GB, Roake J, Merriman TR, Oszkinis G, Galora S, Saracini C, Abbate R, Pulli R, Pratesi C, Saratzis A, Verissimo A, Bumpstead SJ, Badger SA, Clough RE, Cockerill GW, Hafez H, Scott DJ, Futers TS, Romaine SP, Bridge K, Griffin KJ, Bailey MA, Smith A, Thompson MM, van Bockxmeer F, Matthiasson SE, Thorleifsson G, Thorsteinsdottir U, Blankensteijn JD, Teijink JA, Wijmenga C, de Graaf J, Kiemeney LA, Lindholt JS, Hughes AE, Bradley DT, Stirrups K, Golledge J, Norman PE, Powell JT, Humphries SE, Hamby SE, Goodall AH, Nelson CP, Sakalihasan N, Courtois A, Ferrell RE, Eriksson P, Folkersen L, Franco-Cereceda A, Eicher JD, Johnson AD, Betsholtz C, Ruusalepp A, Franzen O, Schadt E, Bjorkegren JL, Lipovich L, Drolet AM, Verhoeven E, Zeebregts CJ, Geelkerken RH, van Sambeek MR, van Sterkenburg SM, de Vries JP, Stefansson K, Thompson JR, de Bakker PI, Deloukas P, Sayers RD, Harrison S, van Rij AM, Samani NJ, Bown MJ

**Rationale:** Abdominal aortic aneurysm (AAA) is a complex disease with both genetic and environmental risk factors. Together, 6 previously identified risk loci only explain a small proportion of the heritability of AAA.
**Objective:** To identify additional AAA risk loci using data from all available genome-wide association studies (GWAS).

**Methods and results:** Through a meta-analysis of 6 GWAS datasets and a validation study totalling 10,204 cases and 107,766 controls we identified 4 new AAA risk loci: 1q32.3 (SMYD2), 13q12.11 (LINC00540), 20q13.12 (near PCIF1/MMP9/ZNF335), and 21q22.2 (ERG). In various database searches we observed no new associations between the lead AAA SNPs and coronary artery disease, blood pressure, lipids or diabetes. Network analyses identified ERG, IL6R and LDLR as modifiers of MMP9, with a direct interaction between ERG and MMP9.
**Conclusions:** The 4 new risk loci for AAA appear to be specific for AAA compared with other cardiovascular diseases and related traits suggesting that traditional cardiovascular risk factor management may only have limited value in preventing the progression of aneurysmal disease.

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Impact factor: 13.965

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**13. Implementation of a standardized protocol to manage elderly patients with low energy pelvic fractures: can service improvement be expected?**
Kanakaris NK, Greven T, West RM, Van Vugt AB, Giannoudis PV

**Purpose:** The incidence of low energy pelvic fractures (FPFs) in the elderly is increasing. Comorbidities, decreased bone-quality, problematic fracture fixation and poor compliance represent some of their specific difficulties. In the absence of uniform management, a standard operating procedure (SOP) was introduced to our unit, aiming to improve the quality of services provided to these patients.
**Methods:** A cohort study was contacted to test the impact of (1) using a specific clinical algorithm and (2) using different antiosteoporotic drugs. Multivariate regression analysis was used to determine prognostic factors. Study endpoints were the time-to-healing, length-of-stay, return to pre-injury mobility, union status, mortality and complications.
**Results:** A total of 132 elderly patients (>/=65 years) admitted during the period 2012-2014 with FPFs were enrolled. High-energy fractures, acetabular fractures, associated trauma affecting mobility, pathological pelvic lesions and operated FPFs were used as exclusion criteria. The majority of included patients were females (108/132; 81.8%), and the mean age was 85.8 years (range 67-108). Use of antiosteoporotics was associated with a shorter time of healing ($p = 0.036$). Patients treated according to the algorithm showed a significant protection against malunion ($p < 0.001$). Also, adherence to the algorithm allowed more patients to return to their pre-injury mobility status ($p = 0.039$).
**Conclusions:** The use of antiosteoporotic medication in elderly patients with fragility pelvic fractures was associated with faster healing, whilst the adherence to a

structured clinical pathway led to less malunions and non-unions and return to pre-injury mobility state.

Gepubliceerd: Int Orthop 2017 Jul 21;41(9):1813-24
Impact factor: 2.520

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**14. Diagnosis and treatment of chronic mesenteric ischemia: An update**
Kolkman JJ, Geelkerken RH

Although the prevalence of mesenteric artery stenoses (MAS) is high, symptomatic chronic mesenteric ischemia (CMI) is rare. The collateral network in the mesenteric circulation, a remnant of the extensive embryonal vascular network, serves to prevent most cases of ischemia. This explains the high incidence of MAS and relative rarity of cases of CMI. The number of affected vessels is the major determinant in CMI development. Most subjects with single vessel mesenteric stenosis do not develop ischemic complaints. Our experience is that most subjects with CA and SMA stenoses with abdominal complaints have CMI. A special mention should be made on patients with median arcuate ligament compression (MALS). There is ongoing debate whether the intermittent compression, caused by respiration movement, can cause ischemic complaints. The arguments pro and con treatment of MALS will be discussed. The clinical presentation of CMI consists of postprandial pain, weight loss, and an adapted eating pattern caused by fear of eating. In end-stage disease more continuous pain, diarrhea or a dyspepsia-like presentation can be observed. Workup of patients suspected for CMI consists of three elements: the anamnesis, the vascular anatomy and proof of ischemia. The main modalities to establish mesenteric vessel patency are duplex ultrasound, CT angiography or MR angiography. Assessing actual ischemia is still challenging, with only tonometry and visual light spectroscopy as tested candidates. Treatment consists of limiting metabolic demand, treatment of the atherosclerotic process and endovascular or operative revascularisation. Metabolic demand can be reduced by using smaller and more frequent meals, proton pump inhibition. Treatment of the atherosclerotic process consists of cessation of smoking, treatment of dyslipidemia, hypertension, hyperglycaemia, and medication with trombocyte aggregation inhibitors.

Gepubliceerd: Best Pract Res Clin Gastroenterol 2017 Feb;31(1):49-57
Impact factor: 3.762

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**15. Medical therapy and intervention do not improve uncomplicated isolated mesenteric artery dissection outcomes over observation alone**

Loeffler JW, Obara H, Fujimura N, Bove P, Newton DH, Zettervall SL, van Petersen AS, Geelkerken RH, Charlton-Ouw KM, Shalhub S, Singh N, Roussel A, Glebova NO, Harlander-Locke MP, Gasper WJ, Humphries MD, Lawrence PF

**Objective:** Isolated dissection of the mesenteric vessels is rare but increasingly recognized. This study aimed to evaluate patient characteristics, primary treatment, and subsequent outcomes of mesenteric dissection using multi-institutional data.
**Methods:** All patients at participant hospitals between January 2003 and December 2015 with dissection of the celiac artery (or its branches) or dissection of the superior mesenteric artery (SMA) were included. Patients with an aortic dissection were excluded. Demographic, treatment, and follow-up data were collected. The primary outcomes included late vessel thrombosis (LVT) and aneurysmal degeneration (AD).
**Results:** Twelve institutions identified 227 patients (220 with complete treatment records) with a mean age of 55 +/- 12.5 years. Median time to last follow up was 15 months (interquartile range, 3.8-32). Most patients were men (82% vs 18% women) and symptomatic at presentation (162 vs 65 asymptomatic). Isolated SMA dissection was more common than celiac artery dissection (n = 158 and 81, respectively). Concomitant dissection of both arteries was rare (n = 12). The mean dissection length was significantly longer in symptomatic patients than in asymptomatic patients in both the celiac artery (27 vs 18 mm; P = .01) and the SMA (64 vs 40 mm; P < .001). Primary treatment was medical in 146 patients with oral anticoagulation or antiplatelet therapy (n = 76 and 70, respectively), whereas 56 patients were observed. LVT occurred in six patients, and 16 patients developed AD (3% and 8%, respectively). For symptomatic patients without evidence of ischemia (n = 134), there was no difference in occurrence of LVT with medical therapy compared with observation alone (9% vs 0%; P = .35). No asymptomatic patient (n = 64) had an episode of LVT at 5 years. AD rates did not differ among symptomatic patients without ischemia treated with medical therapy or observed (9% vs 5%; P = .95). Surgical or endovascular intervention was performed in 18 patients (3 ischemia, 13 pain, 1 AD, 1 asymptomatic). Excluding the patients treated for ischemia, there was no difference in LVT with surgical intervention vs medical management (one vs five; P = .57).
**Conclusions:** Asymptomatic patients with isolated mesenteric artery dissection may be observed and followed up with intermittent imaging. Symptomatic patients tend to have longer dissections than asymptomatic patients. Symptomatic isolated mesenteric artery dissection without evidence of ischemia does not require anticoagulation and may be treated with antiplatelet therapy or observation alone.

Gepubliceerd: J Vasc Surg 2017 Jul;66(1):202-8
Impact factor: 3.536

**16. Higher incidence rates than previously known in tenosynovial giant cell tumors**
Mastboom MJL, Verspoor FGM, Verschoor AJ, Uittenbogaard D, Nemeth B, Mastboom WJB, Bovee JVMG, Dijkstra PDS, Schreuder HWB, Gelderblom H, Van de Sande MAJ

**Background and purpose:** Tenosynovial giant cell tumors (TGCT) are rare, benign tumors, arising in synovial lining of joints, tendon sheaths, or bursae. 2 types are distinguished: localized, either digits or extremity, and diffuse lesions. Current TGCT incidence is based on 1 single US-county study in 1980, with an incidence of 9 and 2 per million person-years in localized (including digits) and diffuse TGCT, respectively. We aim to determine nationwide and worldwide incidence rates (IR) in TGCT affecting digits, localized-extremity TGCT and diffuse-type TGCT.
**Material and methods**: Over a 5-year period, the Dutch Pathology Registry (PALGA) identified 4,503 pathology reports on TGCT. Reports affecting digits were solely used for IR calculations. Reports affecting extremities were clinically evaluated. Dutch IRs were converted to world population IRs.
**Results:** 2,815 (68%) digits, 933 (23%) localized-extremity and 390 (9%) diffuse-type TGCT were identified. Dutch IR in digits, localized-extremity, and diffuse-type TGCT was 34, 11 and 5 per million person-years, respectively. All 3 groups showed a female predilection and highest number of new cases in age category 40-59 years. The knee joint was most often affected: localized-extremity (46%) and diffuse-type (64%) TGCT, mostly treated with open resection: localized (65%) and diffuse (49%). Reoperation rate due to local recurrence for localized-extremity was 9%, and diffuse TGCT 23%. **Interpretation:** This first nationwide study and detailed analyses of IRs in TGCT estimated a worldwide IR in digits, localized-extremity and diffuse TGCT of 29, 10, and 4 per million person-years, respectively. Recurrence rate in diffuse type is 2.6 times higher, compared with localized extremity. TGCT is still considered a rare disease; however, it is more common than previously understood.

Gepubliceerd: Acta Orthop 2017 Dec;88(6):688-94
Impact factor: 3.446

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**17. Atmospheric Pressure and Abdominal Aortic Aneurysm Rupture: Results From a Time Series Analysis and Case-Crossover Study**
Penning de Vries BBL, Kolkert JLP, Meerwaldt R, Groenwold RHH

**Background:** Associations between atmospheric pressure and abdominal aortic aneurysm (AAA) rupture risk have been reported, but empirical evidence is

inconclusive and largely derived from studies that did not account for possible nonlinearity, seasonality, and confounding by temperature.
**Methods:** Associations between atmospheric pressure and AAA rupture risk were investigated using local meteorological data and a case series of 358 patients admitted to hospital for ruptured AAA during the study period, January 2002 to December 2012. Two analyses were performed-a time series analysis and a case-crossover study.
**Results:** Results from the 2 analyses were similar; neither the time series analysis nor the case-crossover study showed a significant association between atmospheric pressure ( P = .627 and P = .625, respectively, for mean daily atmospheric pressure) or atmospheric pressure variation ( P = .464 and P = .816, respectively, for 24-hour change in mean daily atmospheric pressure) and AAA rupture risk.
**Conclusion:** This study failed to support claims that atmospheric pressure causally affects AAA rupture risk. In interpreting our results, one should be aware that the range of atmospheric pressure observed in this study is not representative of the atmospheric pressure to which patients with AAA may be exposed, for example, during air travel or travel to high altitudes in the mountains. Making firm claims regarding these conditions in relation to AAA rupture risk is difficult at best. Furthermore, despite the fact that we used one of the largest case series to date to investigate the effect of atmospheric pressure on AAA rupture risk, it is possible that this study is simply too small to demonstrate a causal link.

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Impact factor: 1.094

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**18. Tumor-stroma ratio as prognostic factor for survival in rectal adenocarcinoma: A retrospective cohort study**
Scheer R, Baidoshvili A, Zoidze S, Elferink MAG, Berkel AEM, Klaase JM, van Diest PJ

**Aim:** To evaluate the prognostic value of the tumor-stroma ratio (TSR) in rectal cancer.
**Methods:** TSR was determined on hematoxylin and eosin stained histological sections of 154 patients treated for rectal adenocarcinoma without prior neoadjuvant treatment in the period 1996-2006 by two observers to assess reproducibility. Patients were categorized into three categories: TSR-high [carcinoma percentage (CP) >/= 70%], TSR-intermediate (CP 40%, 50% and 60%) and TSR-low (CP </= 30%). The relation between categorized TSR and survival was analyzed using Cox proportional hazards model.

**Results:** Thirty-six (23.4%) patients were scored as TSR-low, 70 (45.4%) as TSR-intermediate and 48 (31.2%) as TSR-high. TSR had a good interobserver agreement (kappa = 0.724, concordance 82.5%). Overall survival (OS) and disease free survival (DFS) were significantly better for patients with a high TSR (P = 0.01 and P = 0.02, respectively). A similar association existed for disease specific survival (P = 0.06). In multivariate analysis, patients without lymph node metastasis and an intermediate TSR had a higher risk of dying from rectal cancer (HR = 5.27, 95%CI: 1.54-18.10), compared to lymph node metastasis negative patients with a high TSR. This group also had a worse DFS (HR = 6.41, 95%CI: 1.84-22.28). An identical association was seen for OS. These relations were not seen in lymph node metastasis positive patients.
**Conclusion:** The TSR has potential as a prognostic factor for survival in surgically treated rectal cancer patients, especially in lymph node negative cases.

Gepubliceerd: World J Gastrointest Oncol 2017 Dec 15;9(12):466-74
Impact factor: 0

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**19. Increased migration of antigen presenting cells to newly-formed lymphatic vessels in transplanted kidneys by glycol-split heparin**
Talsma DT, Katta K, Boersema M, Adepu S, Naggi A, Torri G, Stegeman C, Navis G, van Goor H, Hillebrands JL, Yazdani S, van den Born J

**Background:** Chronic renal transplant dysfunction is characterized by loss of renal function and tissue remodeling, including chronic inflammation and lymph vessel formation. Proteoglycans are known for their chemokine presenting capacity. We hypothesize that interruption of the lymphatic chemokine-proteoglycan interaction interferes with the lymphatic outflow of leukocytes from the renal graft and might decrease the anti-graft allo-immune response.
**Methods:** In a rat renal chronic transplant dysfunction model (female Dark-Agouti to male Wistar Furth), chemokines were profiled by qRT-PCR in microdissected tubulo-interstitial tissue. Disruption of lymphatic chemokine-proteoglycan interaction was studied by (non-anticoagulant) heparin-derived polysaccharides in vitro and in renal allografts. The renal allograft function was assessed by rise in plasma creatinine and urea.
**Results:** Within newly-formed lymph vessels of transplanted kidneys, numerous CD45+ leukocytes were found, mainly MHCII+, ED-1-, IDO-, HIS14-, C.

Gepubliceerd: PLoS One 2017;12(6):e0180206
Impact factor: 2.806

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**20. The bittersweet taste of tubulo-interstitial glycans**
Talsma DT, Daha MR, van den Born J

Recently, interesting work was published by Farrar et al. [1] showing the interaction of fucosylated glycoproteins on stressed tubular epithelial cells with collectin-11 leading to complement activation via the lectin route of complement. This elegant work stimulated us to evaluate the dark side (bittersweet taste) of tubulo-interstitial glycans in kidney tissue damage. As will be discussed, glycans not only initiate tubular complement activation but also orchestrate tubulo-interstitial leucocyte recruitment and growth factor responses. In this review we restrict ourselves to tubulo-interstitial damage mainly by proteinuria, ischaemia-reperfusion injury and transplantation, and we discuss the involvement of endothelial and tubular glycans in atypical and Escherichia coli-mediated haemolytic uraemic syndrome. As will be seen, fucosylated, mannosylated, galactosylated and sialylated oligosaccharide structures along with glycosaminoglycans comprise the most important glycans related to kidney injury pathways. Up to now, therapeutic interventions in these glycan-mediated injury pathways are underexplored and warrant further research.

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Impact factor: 4.470

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**21. Colon ischemia: Right-sided colon involvement has a different presentation, etiology and worse outcome. A large retrospective cohort study in histology proven patients**
Ten Heggeler LB, van Dam LJ, Bijlsma A, Visschedijk MC, Geelkerken RH, Meijssen MA, Kolkman JJ

**Background:** Colon ischemia (CI), is generally considered a non-occlusive mesenteric ischemia disorder that usually runs a benign course, but right-sided involvement (RCI) has been associated with worse outcome. The poor outcome of RCI has been associated with comorbidity, but more recently also with occlusions of the mesenteric arteries. We performed a retrospective analysis of a large cohort of CI-patients to assess differences in presentation, etiology, and comorbidity between right-sided colon ischemia (RCI) and non-right-sided colon ischemia (NRCI), and their relation to outcome.
**Methods:** We performed a retrospective cohort study in two centers from 2000 to 2011 for CI and analyzed clinical presentation, etiology, treatment and outcome. Diagnosis was based on full colonoscopy and/or surgical findings and confirmed by histopathology.

**Results:** 239 patients were included (mean age 69, 52% female). RCI was found in 48% and NRCI in 52%. Patients with NRCI presented more often with rectal bleeding (87% vs. 45%; p<0.001). In RCI more nausea (58% vs. 39%; p=0.013), weight loss (56% vs. 19%; p<0.001), paralytic ileus (32% vs. 18%; p=0.018) and peritoneal signs (27% vs. 7%; p<0.001) was observed compared to NRCI. The cause of CI was more often idiopathic in NRCI (46% vs. 26%; p=0.002); an occlusive cause was seen more often in RCI (26.3 vs 2.4%, p<0.0001). RCI patients had longer hospital stay (15 vs. 8 days, p<0.001), need for surgery (61% vs. 34%, p<0.001), and trend toward higher 30-day in-hospital mortality (20% vs. 12%, p=0.084).
**Conclusions:** RCI ischemia has different etiology, presentation, and outcome. The series shows a high proportion of - treatable - vessel occlusion. It reinforces the advice to perform CT angiography in RCI as means to improve its poor outcome.

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Impact factor: 3.762

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**22. Clinical significance of mesenteric arterial collateral circulation in patients with celiac artery compression syndrome**
van Petersen AS, Kolkman JJ, Gerrits DG, van der Palen J, Zeebregts CJ, Geelkerken RH

**Objective:** Although extensive collateral arterial circulation will prevent ischemia in most patients with stenosis of a single mesenteric artery, mesenteric ischemia may occur in these patients, for example, in patients with celiac artery compression syndrome (CACS). Variation in the extent of collateral circulation may explain the difference in clinical symptoms and variability in response to therapy; however, evidence is lacking. The objective of the study was to classify the presence of mesenteric arterial collateral circulation in patients with CACS and to evaluate the relation with clinical improvement after treatment.
**Methods:** Collateral mesenteric circulation was classified on the basis of angiographic findings. Collaterals were categorized in three groups: no visible collaterals (grade 0), collaterals seen on selective angiography only (grade 1), and collaterals visible on nonselective angiography (grade 2). Surgical release of the celiac artery in patients with suspected CACS was performed by arcuate ligament release. Clinical success after surgical revascularization was defined as an improvement in abdominal pain.
**Results:** Between 2002 and 2013, there were 135 consecutive patients with suspected CACS who were operated on. In 129 patients, preoperative angiograms allowed classification of collateral circulation. Primary assisted anatomic success was 93% (120/129). In patients with grade 0 collaterals, clinical success was 81% (39 of

48 patients); with grade 1 collaterals, 89% (25 of 28 patients); and with grade 2 collaterals, 52% (23 of 44 patients; P < .001).
**Conclusions:** Patients with CACS and with extensive collateral mesenteric arterial circulation are less likely to benefit from arcuate ligament release than are patients without this type of collateral circulation. The classification of the extent of mesenteric collateral circulation may predict and guide shared decision-making in patients with CACS.

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Impact factor: 3.536

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**23. Nationwide prospective audit of pancreatic surgery: design, accuracy, and outcomes of the Dutch Pancreatic Cancer Audit**
van Rijssen LB, Koerkamp BG, Zwart MJ, Bonsing BA, Bosscha K, van Dam RM, van Eijck CH, Gerhards MF, van der Harst E, de Hingh IH, de Jong KP, Kazemier G, Klaase J, van Laarhoven CJ, Molenaar IQ, Patijn GA, Rupert CG, van Santvoort HC, Scheepers JJ, van der Schelling GP, Busch OR, Besselink MG, Dutch Pancreatic Cancer Group

**Background:** Auditing is an important tool to identify practice variation and 'best practices'. The Dutch Pancreatic Cancer Audit is mandatory in all 18 Dutch centers for pancreatic surgery.
**Methods:** Performance indicators and case-mix factors were identified by a PubMed search for randomized controlled trials (RCT's) and large series in pancreatic surgery. In addition, data dictionaries of two national audits, three institutional databases, and the Dutch national cancer registry were evaluated. Morbidity, mortality, and length of stay were analyzed of all pancreatic resections registered during the first two audit years. Case ascertainment was cross-checked with the Dutch healthcare inspectorate and key-variables validated in all centers.
**Results:** Sixteen RCT's and three large series were found. Sixteen indicators and 20 case-mix factors were included in the audit. During 2014-2015, 1785 pancreatic resections were registered including 1345 pancreatoduodenectomies. Overall in-hospital mortality was 3.6%. Following pancreatoduodenectomy, mortality was 4.1%, Clavien-Dindo grade >/= III morbidity was 29.9%, median (IQR) length of stay 12 (9-18) days, and readmission rate 16.0%. In total 97.2% of >40,000 variables validated were consistent with the medical charts.
**Conclusions:** The Dutch Pancreatic Cancer Audit, with high quality data, reports good outcomes of pancreatic surgery on a national level.

Gepubliceerd: HPB (Oxford) 2017 Jul 25;19(10):919-26

Impact factor: 3.290

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**24. Low failure rate by means of DLBP fixation of undisplaced femoral neck fractures**
van Walsum ADP, Vroemen J, Janzing HMJ, Winkelhorst T, Kalsbeek J, Roerdink WH

**Background:** This study evaluated the clinical results of a new implant in the internal fixation of undisplaced femoral neck fractures.
**Method:** Irrespective of their age, 149 patients with undisplaced (Garden I and II) femoral neck fractures were included in a prospective multicentre clinical cohort study and were treated by internal fixation by means of the Dynamic Locking Blade Plate (DLBP). The mean age was 69 years and the follow-up at least one year.
**Results:** The DLBP fixation resulted in 6 out of 149 failures caused by AVN (2x), non-union (2x), loss of fixation (3x) or combination of these.
**Conclusion:** The fixation of undisplaced femoral neck fractures by the DLBP resulted in a low failure rate of 4 %.

Gepubliceerd: Eur J Trauma Emerg Surg 2017 Aug;43(4):475-80
Impact factor: 0.895

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**25. A phantom study for the comparison of different brands of computed tomography scanners and software packages for endovascular aneurysm repair sizing and planning**
Velu JF, Groot Jebbink E, de Vries JP, van der Palen JA, Slump CH, Geelkerken RH

**Objectives:** Correct sizing of endoprostheses used for the treatment of abdominal aortic aneurysms is important to prevent endoleaks and migration. Sizing requires several steps and each step introduces a possible sizing error. The goal of this study was to investigate the magnitude of these errors compared to the golden standard: a vessel phantom. This study focuses on the errors in sizing with three different brands of computed tomography angiography scanners in combination with three reconstruction software packages.
**Methods:** Three phantoms with a different diameter, altitude and azimuth were scanned with three computed tomography scanners: Toshiba Aquilion 64-slice, Philips Brilliance iCT 256-slice and Siemens Somatom Sensation 64-slice. The phantom diameters were determined in the stretched view after central lumen line reconstruction by three observers using Simbionix PROcedure Rehearsal Studio, 3mensio and TeraRecon planning software. The observers, all novices in sizing

endoprostheses using planning software, measured 108 slices each. Two senior vascular surgeons set the tolerated error margin of sizing on +/-1.0 mm.
**Results:** In total, 11.3% of the measurements (73/648) were outside the set margins of +/-1.0 mm from the phantom diameter, with significant differences between the scanner types (14.8%, 12.1%, 6.9% for the Siemens scanner, Philips scanner and Toshiba scanner, respectively, p-value = 0.032), but not between the software packages (8.3%, 11.1%, 14.4%, p-value = 0.141) or the observers (10.6%, 9.7%, 13.4%, p-value = 0.448).
**Conclusions:** It can be concluded that the errors in sizing were independent of the used software packages, but the phantoms scanned with Siemens scanner were significantly more measured incorrectly than the phantoms scanned with the Toshiba scanner. Consequently, awareness on the type of computed tomography scanner and computed tomography scanner setting is necessary, especially in complex abdominal aortic aneurysms sizing for fenestrated or branched endovascular aneurysm repair if appropriate the sizing is of upmost importance.

Gepubliceerd: Vascular 2017 Jan 1;1708538117726648
Impact factor: 0.733

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**26. Validation of the Simbionix PROcedure Rehearsal Studio sizing module: A comparison of software for endovascular aneurysm repair sizing and planning**
Velu JF, Groot JE, de Vries JP, Slump CH, Geelkerken RH

An important determinant of successful endovascular aortic aneurysm repair is proper sizing of the dimensions of the aortic-iliac vessels. The goal of the present study was to determine the concurrent validity, a method for comparison of test scores, for EVAR sizing and planning of the recently introduced Simbionix PROcedure Rehearsal Studio (PRORS). Seven vascular specialists analyzed anonymized computed tomography angiography scans of 70 patients with an infrarenal aneurysm of the abdominal aorta, using three different sizing software packages Simbionix PRORS (Simbionix USA Corp., Cleveland, OH, USA), 3mensio (Pie Medical Imaging BV, Maastricht, The Netherlands), and TeraRecon (Aquarius, Foster City, CA, USA). The following measurements were included in the protocol: diameter 1 mm below the most distal main renal artery, diameter 15 mm below the lowest renal artery, maximum aneurysm diameter, and length from the most distal renal artery to the left iliac artery bifurcation. Averaged over the locations, the intraclass correlation coefficient is 0.83 for Simbionix versus 3mensio, 0.81 for Simbionix versus TeraRecon, and 0.86 for 3mensio versus TeraRecon. It can be concluded that the Simbionix sizing software is as precise as two other validated and commercially available software packages.

Gepubliceerd: Vascular 2017;25(1):80-5
Impact factor: 0.733

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**27. Survival analysis of the CEAwatch multicentre clustered randomized trial**
Verberne CJ, Zhan Z, van den Heuvel ER, Oppers F, de Jong AM, Grossmann I, Klaase JM, de Bock GH, Wiggers T

**Background:** The CEAwatch randomized trial showed that follow-up with intensive carcinoembryonic antigen (CEA) monitoring (CEAwatch protocol) was better than care as usual (CAU) for early postoperative detection of colorectal cancer recurrence. The aim of this study was to calculate overall survival (OS) and disease-specific survival (DSS).
**Methods:** For all patients with recurrence, OS and DSS were compared between patients detected by the CEAwatch protocol versus CAU, and by the method of detection of recurrence, using Cox regression models.
**Results:** Some 238 patients with recurrence were analysed (7.5 per cent); a total of 108 recurrences were detected by CEA blood test, 64 (55.2 per cent) within the CEAwatch protocol and 44 (41.9 per cent) in the CAU group (P = 0.007). Only 16 recurrences (13.8 per cent) were detected by patient self-report in the CEAwatch group, compared with 33 (31.4 per cent) in the CAU group. There was no significant improvement in either OS or DSS with the CEAwatch protocol compared with CAU: hazard ratio 0.73 (95 per cent 0.46 to 1.17) and 0.78 (0.48 to 1.28) respectively. There were no differences in survival when recurrence was detected by CT versus CEA measurement, but both of these methods yielded better survival outcomes than detection by patient self-report.
**Conclusion:** There was no direct survival benefit in favour of the intensive programme, but the CEAwatch protocol led to a higher proportion of recurrences being detected by CEA-based blood test and reduced the number detected by patient self-report. This is important because detection of recurrence by blood test was associated with significantly better survival than patient self-report, indirectly supporting use of the CEAwatch protocol.

Gepubliceerd: Br J Surg 2017 Jul;104(8):1069-77
Impact factor: 5.899

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**28. Consistency of patient-reported outcomes after cholecystectomy and their implications on current surgical practice: a prospective multicenter cohort study**

Wennmacker S, Lamberts M, Gerritsen J, Roukema JA, Westert G, Drenth J, van Laarhoven C

**Background:** Persistent postoperative pain (up to 41 %) and significant practice variation necessitate better patient selection for cholecystectomy. Patient-reported outcome measures (PROMs) are nowadays known to serve as a tool for better patient selection, although variability within these subjective outcomes may be a point for debate. This study determines associations of both the preoperative pain and patient characteristics with PROMs at 24 weeks after cholecystectomy. In order to evaluate variability of PROMs, we also determined consistency of these outcomes in time.
**Methods:** This prospective multicenter cohort study included adult patients diagnosed with uncomplicated symptomatic cholecystolithiasis. Twenty-four weeks after surgery, a questionnaire study was carried out, containing Gastrointestinal Quality of Life Index (GIQLI) and Patients' Experience of Surgery Questionnaire. Results were compared to preoperative data and results 12 weeks post-cholecystectomy. Logistic regression analyses were performed to determine associations. Additional post hoc analysis on associations between preoperative selection criteria and PROMs was done.
**Results:** A total of 360 patients (85 %) responded. Postoperative absence of pain was reported by 59.2 %. Associated characteristics were symptoms </=1 year prior to surgery [OR 1.85 (95 % CI 1.11-3.09)] and high baseline GIQLI score [OR 1.04 (95 % CI 1.02-1.05)]. General improvement in abdominal symptoms and positive result of surgery were found in 90 %; no preoperative variables were significantly associated. PROMs showed consistency at 12 and 24 weeks postoperatively. Post hoc analysis showed no significant associations.
**Conclusion:** PROM-based preoperative selection criteria need to be considered to select those patients who achieve freedom of pain after surgical treatment of uncomplicated symptomatic cholecystolithiasis. Other patients might consider cholecystectomy as successful, but are less likely to be free of pain. Usefulness of PROMs is underscored as they proved to be consistent in time in evaluating surgical outcome.

Gepubliceerd: Surg Endosc 2017 Jan;31(1):215-24
Impact factor: 3.747

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**29. Randomized clinical trial of open versus laparoscopic left lateral hepatic sectionectomy within an enhanced recovery after surgery programme (ORANGE II study)**

Wong-Lun-Hing EM, van Dam RM, van Breukelen GJ, Tanis PJ, Ratti F, van Hillegersberg R, Slooter GD, de Wilt JH, Liem MS, de Boer MT, Klaase JM, Neumann UP, Aldrighetti LA, Dejong CH

**Background:** Laparoscopic left lateral sectionectomy (LLLS) has been associated with shorter hospital stay and reduced overall morbidity compared with open left lateral sectionectomy (OLLS). Strong evidence has not, however, been provided.
**Methods:** In this multicentre double-blind RCT, patients (aged 18-80 years with a BMI of 18-35 kg/m2 and ASA fitness grade of III or below) requiring left lateral sectionectomy (LLS) were assigned randomly to OLLS or LLLS within an enhanced recovery after surgery (ERAS) programme. All randomized patients, ward physicians and nurses were blinded to the procedure undertaken. A parallel prospective registry (open non-randomized (ONR) versus laparoscopic non-randomized (LNR)) was used to monitor patients who were not enrolled for randomization because of doctor or patient preference. The primary endpoint was time to functional recovery. Secondary endpoints were length of hospital stay (LOS), readmission rate, overall morbidity, composite endpoint of liver surgery-specific morbidity, mortality, and reasons for delay in discharge after functional recovery.
**Results:** Between January 2010 and July 2014, patients were recruited at ten centres. Of these, 24 patients were randomized at eight centres, and 67 patients from eight centres were included in the prospective registry. Owing to slow accrual, the trial was stopped on the advice of an independent Data and Safety Monitoring Board in the Netherlands. No significant difference in median (i.q.r.) time to functional recovery was observed between laparoscopic and open surgery in the randomized or non-randomized groups: 3 (3-5) days for OLLS versus 3 (3-3) days for LLLS; and 3 (3-3) days for ONR versus 3 (3-4) days for LNR. There were no significant differences with regard to LOS, morbidity, reoperation, readmission and mortality rates.
**Conclusion:** This RCT comparing open and laparoscopic LLS in an ERAS setting was not able to reach a conclusion on time to functional recovery, because it was stopped prematurely owing to slow accrual. Registration number: NCT00874224 ( https://www.clinicaltrials.gov)¶

Br J Surg 2017 Apr;104(5):525-35
Impact factor: 5.899

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**30. An International Collaborative Standardizing a Comprehensive Patient-Centered Outcomes Measurement Set for Colorectal Cancer**
Zerillo JA, Schouwenburg MG, van Bommel ACM, Stowell C, Lippa J, Bauer D, Berger AM, Boland G, Borras JM, Buss MK, Cima R, Van Cutsem E, van Duyn EB, Finlayson SRG, Hung-Chun CS, Langelotz C, Lloyd J, Lynch AC, Mamon HJ,

McAllister PK, Minsky BD, Ngeow J, Abu Hassan MR, Ryan K, Shankaran V, Upton MP, Zalcberg J, van de Velde CJ, Tollenaar R

**Importance:** Global health systems are shifting toward value-based care in an effort to drive better outcomes in the setting of rising health care costs. This shift requires a common definition of value, starting with the outcomes that matter most to patients.
**Objective:** The International Consortium for Health Outcomes Measurement (ICHOM), a nonprofit initiative, was formed to define standard sets of outcomes by medical condition. In this article, we report the efforts of ICHOM's working group in colorectal cancer.
**Evidence Review:** The working group was composed of multidisciplinary oncology specialists in medicine, surgery, radiation therapy, palliative care, nursing, and pathology, along with patient representatives. Through a modified Delphi process during 8 months (July 8, 2015 to February 29, 2016), ICHOM led the working group to a consensus on a final recommended standard set. The process was supported by a systematic PubMed literature review (1042 randomized clinical trials and guidelines from June 3, 2005, to June 3, 2015), a patient focus group (11 patients with early and metastatic colorectal cancer convened during a teleconference in August 2015), and a patient validation survey (among 276 patients with and survivors of colorectal cancer between October 15, 2015, and November 4, 2015). Findings: After consolidating findings of the literature review and focus group meeting, a list of 40 outcomes was presented to the WG and underwent voting. The final recommendation includes outcomes in the following categories: survival and disease control, disutility of care, degree of health, and quality of death. Selected case-mix factors were recommended to be collected at baseline to facilitate comparison of results across treatments and health care professionals.
**Conclusions:** A standardized set of patient-centered outcome measures to inform value-based health care in colorectal cancer was developed. Pilot efforts are under way to measure the standard set among members of the working group.

Gepubliceerd: JAMA Oncol 2017 May 1;3(5):686-94
Impact factor: 16.559

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Totale impact factor: 115.536
Gemiddelde impact factor: 3.851

Aantal artikelen 1e, 2e of laatste auteur: 11
Totale impact factor: 29.646
Gemiddelde impact factor: 2.695

# Intensive Care

**1. Critical Illness-Related Corticosteroid Insufficiency (CIRCI): A Narrative Review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM)**
Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J, Carcillo J, Christ-Crain M, Cooper MS, Marik PE, Meduri GU, Olsen KM, Rochwerg B, Rodgers SC, Russell JA, Van den Berghe G

**Objective:** To provide a narrative review of the latest concepts and understanding of the pathophysiology of critical illness-related corticosteroid insufficiency (CIRCI).
**Participants:** A multi-specialty task force of international experts in critical care medicine and endocrinology and members of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine.
**Data sources:** Medline, Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews.
**Results:** Three major pathophysiologic events were considered to constitute CIRCI: dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, altered cortisol metabolism, and tissue resistance to glucocorticoids. The dysregulation of the HPA axis is complex, involving multidirectional crosstalk between the CRH/ACTH pathways, autonomic nervous system, vasopressinergic system, and immune system. Recent studies have demonstrated that plasma clearance of cortisol is markedly reduced during critical illness, explained by suppressed expression and activity of the primary cortisol-metabolizing enzymes in the liver and kidney. Despite the elevated cortisol levels during critical illness, tissue resistance to glucocorticoids is believed to occur due to insufficient glucocorticoid alpha-mediated anti-inflammatory activity.
**Conclusions:** Novel insights into the pathophysiology of CIRCI add to the limitations of the current diagnostic tools to identify at-risk patients and may also impact how corticosteroids are used in patients with CIRCI.

Gepubliceerd: Crit Care Med 2017 Dec;45(12):2089-98
Impact factor: 7.050

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**2. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017**

Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, Briegel J, Carcillo J, Christ-Crain M, Cooper MS, Marik PE, Meduri GU, Olsen KM, Rodgers SC, Russell JA, Van den Berghe G

**Objective:** To update the 2008 consensus statements for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in adult and pediatric patients.
**Participants:** A multispecialty task force of 16 international experts in critical care medicine, endocrinology, and guideline methods, all of them members of the Society of Critical Care Medicine and/or the European Society of Intensive Care Medicine.
**Design/methods:** The recommendations were based on the summarized evidence from the 2008 document in addition to more recent findings from an updated systematic review of relevant studies from 2008 to 2017 and were formulated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. The strength of each recommendation was classified as strong or conditional, and the quality of evidence was rated from high to very low based on factors including the individual study design, the risk of bias, the consistency of the results, and the directness and precision of the evidence. Recommendation approval required the agreement of at least 80% of the task force members.
**Results:** The task force was unable to reach agreement on a single test that can reliably diagnose CIRCI, although delta cortisol (change in baseline cortisol at 60 min of < 9 mug/dL) after cosyntropin (250 mug) administration and a random plasma cortisol of < 10 mug/dL may be used by clinicians. We suggest against using plasma-free cortisol or salivary cortisol level over plasma total cortisol (conditional, very low quality of evidence). For treatment of specific conditions, we suggest using IV hydrocortisone < 400 mg/day for >/= 3 days at full dose in patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy (conditional, low quality of evidence). We suggest not using corticosteroids in adult patients with sepsis without shock (conditional recommendation, moderate quality of evidence). We suggest the use of IV methylprednisolone 1 mg/kg/day in patients with early moderate to severe acute respiratory distress syndrome (PaO2/FiO2 < 200 and within 14 days of onset) (conditional, moderate quality of evidence). Corticosteroids are not suggested for patients with major trauma (conditional, low quality of evidence).
**Conclusions:** Evidence-based recommendations for the use of corticosteroids in critically ill patients with sepsis and septic shock, acute respiratory distress syndrome, and major trauma have been developed by a multispecialty task force.

Gepubliceerd: Crit Care Med 2017 Dec;45(12):2078-88
Impact factor: 7.050

**3. Quality of life after bone sarcoma surgery around the knee: A long-term follow-up study**
Bekkering WP, van Egmond-van Dam JC, Bramer JAM, Beishuizen A, Fiocco M, Dijkstra PDS

It remains unclear if quality of life (QoL) improvements could be expected in young patients after malignant bone tumour surgery after 2 years. To assess the course of QoL over time during a long-term follow-up, malignant bone tumour survivors of a previous short-term study were included. Assessments were done at least 5 years after surgery. QoL was measured with Short-form (SF)-36, TNO-AZL Questionnaire for Adult's Quality of Life (TAAQOL) and Bone tumour (Bt)-DUX. QoL throughout the follow-up was analysed by linear mixed model analysis. From the original cohort of 44 patients; 20 patients were included for this study, 10 males; mean age at surgery 15.1 years and mean follow-up 7.2 years. Twenty-one patients of the initial cohort (47%) deceased. Fifteen patients (75%) underwent limb-salvage and five (25%) ablative surgery. QoL improved significantly during follow-up at Physical Component Summary Scale scale of the SF-36 and TAAQOL and all subscales of the Bt-DUX ($p < .01$). No significant differences were found between current evaluations and previous evaluations at 2 years after surgery ($p = .41$-$.98$). Significant advantages after limb-salvage were seen at the PCS scale of the SF-36 (MD 13.7, $p = .05$) and the cosmetic scale of the Bt-DUX (MD 17.7, $p = .04$)**.**

Gepubliceerd: Eur J Cancer Care (Engl ) 2017 Jul;26(4)
Impact factor: 2.104

**4. Staging Evaluation and Response Criteria Harmonization (SEARCH) for Childhood, Adolescent and Young Adult Hodgkin Lymphoma (CAYAHL): Methodology statement**
Flerlage JE, Kelly KM, Beishuizen A, Cho S, De Alarcon PA, Dieckmann U, Drachtman RA, Hoppe BS, Howard SC, Kaste SC, Kluge R, Kurch L, Landman-Parker J, Lewis J, Link MP, McCarten K, Punnett A, Stoevesandt D, Voss SD, Wallace WH, Mauz-Korholz C, Metzger ML

International harmonization of staging evaluation and response criteria is needed for childhood, adolescence, and young adulthood Hodgkin lymphoma. Two Hodgkin lymphoma protocols from cooperative trials in Europe and North America were compared for areas in need of harmonization, and an evidence-based approach is currently underway to harmonize staging and response evaluations with a goal to

enhance comparisons, expedite identification of effective therapies, and aid in the approval process for new agents by regulatory agencies**.**

Gepubliceerd: Pediatr Blood Cancer 2017 Jul;64(7)
Impact factor: 2.513

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**5. Impact of single room design on the spread of multi-drug resistant bacteria in an intensive care unit**
Halaby T, Al Naiemi N, Beishuizen B, Verkooijen R, Ferreira JA, Klont R, Vandenbroucke-Grauls C

**Background:** Cross-transmission of nosocomial pathogens occurs frequently in intensive care units (ICU). The aim of this study was to investigate whether the introduction of a single room policy resulted in a decrease in transmission of multidrug-resistant (MDR) bacteria in an ICU.
**Methods:** We performed a retrospective study covering two periods: between January 2002 and April 2009 (old-ICU) and between May 2009 and March 2013 (new-ICU, single-room). These periods were compared with respect to the occurrence of representative MDR Gram-negative bacteria. Routine microbiological screening, was performed on all patients on admission to the ICU and then twice a week. Multi-drug resistance was defined according to a national guideline. The first isolates per patient that met the MDR-criteria, detected during the ICU admission were included in the analysis. To investigate the clonality, isolates were genotyped by DiversiLab (bioMerieux, France) or Amplified Fragment Length Polymorphism (AFLP). To guarantee the comparability of the two periods, the 'before' and 'after' periods were chosen such that they were approximately identical with respect to the following factors: number of admissions, number of beds, bed occupancy rate, per year and month.
**Results:** Despite infection prevention efforts, high prevalence of MRD bacteria continue to occur in the original facility. A marked and sustained decrease in the prevalence of MDR-GN bacteria was observed after the migration to the new ICU, while there appear to be no significant changes in the other variables including bed occupancy and numbers of patient admissions.
**Conclusion:** Single room ICU design contributes significantly to the reduction of cross transmission of MRD-bacteria**.**

Gepubliceerd: Antimicrob Resist Infect Control 2017;6:117
Impact factor: 2.989

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**6. Whole-body MRI reveals high incidence of osteonecrosis in children treated for Hodgkin lymphoma**
Littooij AS, Kwee TC, Enriquez G, Verbeke JI, Granata C, Beishuizen A, de Lange C, Zennaro F, Bruin MC, Nievelstein RA

Osteonecrosis is a well-recognized complication in patients treated with corticosteroids. The incidence of osteonecrosis in children treated for Hodgkin lymphoma is unknown because prospective whole-body magnetic resonance imaging (MRI) studies are lacking in this patient population. Paediatric patients with newly diagnosed Hodgkin lymphoma who were treated according to a uniform paediatric Hodgkin protocol were eligible for inclusion in this prospective study. Whole-body MRI was performed in all 24 included patients (mean age 15.1 years, 12 girls) both before treatment and after 2 cycles of chemotherapy, and in 16 patients after completion of chemotherapy. Osteonecrosis was identified in 10 patients (41.7%, 95% confidence interval: 22.0-61.4%), with a total of 56 osteonecrotic sites. Osteonecrosis was detected in 8 patients after 2 cycles of OEPA (vincristine, etoposide, prednisone, doxorubicin), and in 2 additional patients after completion of chemotherapy. Epiphyseal involvement of long bones was seen in 4 of 10 children. None of the patients with osteonecrosis had any signs of bone collapse at the times of scanning. Whole-body MRI demonstrates osteonecrosis to be a common finding occurring during therapy response assessment of paediatric Hodgkin lymphoma. Detection of early epiphyseal osteonecrosis could allow for treatment before bone collapse and joint damage may occur**.**

Gepubliceerd: Br J Haematol 2017 Feb;176(4):637-42
Impact factor: 5.670

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**7. Limited effect of cooling speed on ECG and electrolytes during therapeutic hypothermia after cardiac arrest**
Nieuwenhuijse EA, Lust EJ, de Groot R, Biermann H, Beishuizen A, Girbes ARJ, de Waard MC

Gepubliceerd: Resuscitation 2017 May;114:e15-e16
Impact factor: 5.230

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**8. Intravenous citrulline generation test to assess intestinal function in intensive care unit patients**
Peters JH, Wierdsma NJ, Beishuizen A, Teerlink T, van Bodegraven AA

**Background:** Assessment of a quantifiable small intestinal function test is cumbersome. Fasting citrulline concentrations have been proposed as a measure of enterocyte function and elaborated into a citrulline generation test (CGT), which is applicable only when glutamine is administered orally. CGT is an oral test, limiting its use, for example, in critically ill patients.
**Objective:** Assessment of normative values and feasibility of an intravenously performed CGT in intensive care unit (ICU) patients with presumed gastrointestinal motility disturbances, especially when performed intravenously.
**Design:** CGT reference values were determined in 16 stable ICU patients using two different CGT methods, namely following either enteral or intravenous glutamine administration and both with simultaneous arterial and venous plasma citrulline sampling at six time-points. Plasma amino acid analysis was performed using reverse-phase high-performance liquid chromatography.
**Results:** The median total generation of citrulline in 90 min (CGT iAUCT90) was markedly higher with arterial citrulline sampling compared with venous citrulline sampling, being 724+/-585 and 556+/-418 micromol/L/min for enteral glutamine, respectively (p=0.02) and 977+/-283 and 769+/-231 micromol/L/min for intravenous glutamine, respectively (p=0.0004). The median slope (time-dependent increase) for plasma arterial and venous citrulline during the CGT was 0.20+/-0.16 and 0.18+/-0.12 micromol/L/min for enteral glutamine, respectively (p=0.004) and 0.22+/-0.16 and 0.19+/-0.05 micromol/L/min for intravenous glutamine, respectively (p=0.02).
**Conclusion:** Intravenous glutamine administration combined with arterial plasma citrulline sampling yielded the least variation in CGT characteristics in stable ICU patients. A 2-point measurement test had comparable test characteristics as a 6-point measurement CGT and seems promising**.**

Gepubliceerd: Clin Exp Gastroenterol 2017;10:75-81
Impact factor: 0

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**9. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections**

Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Kristoffersen KB, Burkhardt O, Welte T, Schroeder S, Nobre V, Wei L, Bucher HC, Bhatnagar N, Annane D, Reinhart K, Branche A, Damas P, Nijsten M, de Lange DW, Deliberato RO, Lima SS, Maravic-Stojkovic V, Verduri A, Cao B, Shehabi Y, Beishuizen A, Jensen JS, Corti C, Van Oers JA, Falsey AR, de JE, Oliveira CF, Beghe B, Briel M, Mueller B

**Background:** Acute respiratory infections (ARIs) comprise of a large and heterogeneous group of infections including bacterial, viral, and other aetiologies. In

recent years, procalcitonin (PCT), a blood marker for bacterial infections, has emerged as a promising tool to improve decisions about antibiotic therapy (PCT-guided antibiotic therapy). Several randomised controlled trials (RCTs) have demonstrated the feasibility of using procalcitonin for starting and stopping antibiotics in different patient populations with ARIs and different settings ranging from primary care settings to emergency departments, hospital wards, and intensive care units. However, the effect of using procalcitonin on clinical outcomes is unclear. This is an update of a Cochrane review and individual participant data meta-analysis first published in 2012 designed to look at the safety of PCT-guided antibiotic stewardship.
**Objectives:** The aim of this systematic review based on individual participant data was to assess the safety and efficacy of using procalcitonin for starting or stopping antibiotics over a large range of patients with varying severity of ARIs and from different clinical settings.
**Search methods:** We searched the Cochrane Central Register of Controlled Trials (CENTRAL), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE, and Embase, in February 2017, to identify suitable trials. We also searched ClinicalTrials.gov to identify ongoing trials in April 2017.
**Selection criteria:** We included RCTs of adult participants with ARIs who received an antibiotic treatment either based on a procalcitonin algorithm (PCT-guided antibiotic stewardship algorithm) or usual care. We excluded trials if they focused exclusively on children or used procalcitonin for a purpose other than to guide initiation and duration of antibiotic treatment.
**Data collection and analysis:** Two teams of review authors independently evaluated the methodology and extracted data from primary studies. The primary endpoints were all-cause mortality and treatment failure at 30 days, for which definitions were harmonised among trials. Secondary endpoints were antibiotic use, antibiotic-related side effects, and length of hospital stay. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using multivariable hierarchical logistic regression adjusted for age, gender, and clinical diagnosis using a fixed-effect model. The different trials were added as random-effects into the model. We conducted sensitivity analyses stratified by clinical setting and type of ARI. We also performed an aggregate data meta-analysis. MAIN
**Results:** From 32 eligible RCTs including 18 new trials for this 2017 update, we obtained individual participant data from 26 trials including 6708 participants, which we included in the main individual participant data meta-analysis. We did not obtain individual participant data for four trials, and two trials did not include people with confirmed ARIs. According to GRADE, the quality of the evidence was high for the outcomes mortality and antibiotic exposure, and quality was moderate for the outcomes treatment failure and antibiotic-related side effects.Primary endpoints: there were 286 deaths in 3336 procalcitonin-guided participants (8.6%) compared to 336 in 3372 controls (10.0%), resulting in a significantly lower mortality associated with

procalcitonin-guided therapy (adjusted OR 0.83, 95% CI 0.70 to 0.99, P = 0.037). We could not estimate mortality in primary care trials because only one death was reported in a control group participant. Treatment failure was not significantly lower in procalcitonin-guided participants (23.0% versus 24.9% in the control group, adjusted OR 0.90, 95% CI 0.80 to 1.01, P = 0.068). Results were similar among subgroups by clinical setting and type of respiratory infection, with no evidence for effect modification (P for interaction > 0.05). Secondary endpoints: procalcitonin guidance was associated with a 2.4-day reduction in antibiotic exposure (5.7 versus 8.1 days, 95% CI -2.71 to -2.15, P < 0.001) and lower risk of antibiotic-related side effects (16.3% versus 22.1%, adjusted OR 0.68, 95% CI 0.57 to 0.82, P < 0.001). Length of hospital stay and intensive care unit stay were similar in both groups. A sensitivity aggregate-data analysis based on all 32 eligible trials showed similar results. AUTHORS'
**Conclusions:** This updated meta-analysis of individual participant data from 12 countries shows that the use of procalcitonin to guide initiation and duration of antibiotic treatment results in lower risks of mortality, lower antibiotic consumption, and lower risk for antibiotic-related side effects. Results were similar for different clinical settings and types of ARIs, thus supporting the use of procalcitonin in the context of antibiotic stewardship in people with ARIs. Future high-quality research is needed to confirm the results in immunosuppressed patients and patients with non-respiratory infections**.**

Gepubliceerd: Cochrane Database Syst Rev 2017 Oct 13;10:CD007498
Impact factor: 6.264

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**10. Early EEG for outcome prediction of postanoxic coma: prospective cohort study with cost-minimization analysis**
Sondag L, Ruijter BJ, Tjepkema-Cloostermans MC, Beishuizen A, Bosch FH, van Til JA, van Putten MJAM, Hofmeijer J

**Background:** We recently showed that electroencephalography (EEG) patterns within the first 24 hours robustly contribute to multimodal prediction of poor or good neurological outcome of comatose patients after cardiac arrest. Here, we confirm these results and present a cost-minimization analysis. Early prognosis contributes to communication between doctors and family, and may prevent inappropriate treatment. METHODS: A prospective cohort study including 430 subsequent comatose patients after cardiac arrest was conducted at intensive care units of two teaching hospitals. Continuous EEG was started within 12 hours after cardiac arrest and continued up to 3 days. EEG patterns were visually classified as unfavorable (isoelectric, low-voltage, or burst suppression with identical bursts) or favorable

(continuous patterns) at 12 and 24 hours after cardiac arrest. Outcome at 6 months was classified as good (cerebral performance category (CPC) 1 or 2) or poor (CPC 3, 4, or 5). Predictive values of EEG measures and cost-consequences from a hospital perspective were investigated, assuming EEG-based decision- making about withdrawal of life-sustaining treatment in the case of a poor predicted outcome.
**Results:** Poor outcome occurred in 197 patients (51% of those included in the analyses). Unfavorable EEG patterns at 24 hours predicted a poor outcome with specificity of 100% (95% CI 98-100%) and sensitivity of 29% (95% CI 22-36%). Favorable patterns at 12 hours predicted good outcome with specificity of 88% (95% CI 81-93%) and sensitivity of 51% (95% CI 42-60%). Treatment withdrawal based on an unfavorable EEG pattern at 24 hours resulted in a reduced mean ICU length of stay without increased mortality in the long term. This gave small cost reductions, depending on the timing of withdrawal.
**Conclusions:** Early EEG contributes to reliable prediction of good or poor outcome of postanoxic coma and may lead to reduced length of ICU stay. In turn, this may bring small cost reductions**.**

Gepubliceerd: Crit Care 2017 May 15;21(1):111
Impact factor: 5.358

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**11. Efficacy of different cooling technologies for therapeutic temperature management: A prospective intervention study**
Sonder P, Janssens GN, Beishuizen A, Henry CL, Rittenberger JC, Callaway CW, Dezfulian C, Polderman KH

**Background:** Mild therapeutic hypothermia (32-36 degrees C) is associated with improved outcomes in patients with brain injury after cardiac arrest (CA). Various devices are available to induce and maintain hypothermia, but few studies have compared the performance of these devices. We performed a prospective study to compare four frequently used cooling systems in inducing and maintaining hypothermia followed by controlled rewarming.
**Methods:** We performed a prospective multi-centered study in ten ICU's in three hospitals within the UPMC health system. Four different cooling technologies (seven cooling methods in total) were studied: two external water-circulating cooling blankets (Meditherm(R) and Blanketrol(R)), gel-coated adhesive cooling pads (Arctic Sun(R)), and endovascular cooling catheters with balloons circulating ice-cold saline (Thermogard(R)). For the latter system we studied three different types of catheter with two, three or four water-circulating balloons, respectively. In contrast to previous studies, we not only studied the cooling rate (i.e., time to target temperature) in the induction phase, but also the percentage of the time during the maintenance phase

that temperature was on target +/-0.5 degrees C, and the efficacy of devices to control rewarming. We believe that these are more important indicators of device performance than induction speed alone.
**Results:** 129 consecutive patients admitted after CA and treated with hypothermia were screened, and 120 were enrolled in the study. Two researchers dedicated fulltime to this study monitored TH treatment in all patients, including antishivering measures, additional cooling measures used (e.g. icepacks and cold fluid infusion), and all other issues related to temperature management. Baseline characteristics were similar for all groups. Cooling rates were 2.06+/-1.12 degrees C/h for endovascular cooling, 1.49+/-0.82 for Arctic sun, 0.61+/-0.36 for Meditherm and 1.22+/-1.12 for Blanketrol. Time within target range +/-0.5 degrees C was 97.3+/-6.0% for Thermogard, 81.8+/-25.2% for Arctic Sun, 57.4+/-29.3% for Meditherm, and 64.5+/-20.1% for Blanketrol. The following differences were significant: Thermogard vs. Meditherm ($p<0.01$), Thermogard vs. Blanketrol ($p<0.01$), and Arctic Sun vs. Meditherm ($p<0.02$). No major complications occurred with any device.
**Conclusions:** Endovascular cooling and gel-adhesive pads provide more rapid hypothermia induction and more effective temperature maintenance compared to water-circulating cooling blankets. This applied to induction speed, but (more importantly) also to time within target range during maintenance**.**

Gepubliceerd: Resuscitation 2017 Dec 26;124:14-20
Impact factor: 5.230

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**12. Understanding the reconstitution of the B-cell compartment in bone marrow and blood after treatment for B-cell precursor acute lymphoblastic leukaemia**
Theunissen PMJ, van den Branden A, Sluijs-Gelling A, De Haas V, Beishuizen A, van Dongen JJM, Van Der Velden VHJ

A better understanding of the reconstitution of the B-cell compartment during and after treatment in B-cell precursor acute lymphoblastic leukaemia (BCP-ALL) will help to assess the immunological status and needs of post-treatment BCP-ALL patients. Using 8-colour flow cytometry and proliferation-assays, we studied the composition and proliferation of both the B-cell precursor (BCP) population in the bone marrow (BM) and mature B-cell population in peripheral blood (PB) during and after BCP-ALL therapy. We found a normal BCP differentiation pattern and a delayed formation of classical CD38dim -naive mature B-cells, natural effector B-cells and memory B-cells in patients after chemotherapy. This B-cell differentiation/maturation pattern was strikingly similar to that during initial B-cell development in healthy infants. Tissue-resident plasma cells appeared to be partly protected from chemotherapy. Also, we found that the fast recovery of naive mature B-cell numbers after chemotherapy was

the result of increased de novo BCP generation, rather than enhanced B-cell proliferation in BM or PB. These results indicate that post-treatment BCP-ALL patients will eventually re-establish a B-cell compartment with a composition and B-cell receptor repertoire similar to that in healthy children. Additionally, the formation of a new memory B-cell compartment suggests that revaccination might be beneficial after BCP-ALL therapy**.**

Gepubliceerd: Br J Haematol 2017 Jul;178(2):267-78
Impact factor: 5.670

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**13. Cerebral Recovery Index: Reliable Help for Prediction of Neurologic Outcome After Cardiac Arrest**

Tjepkema-Cloostermans MC, Hofmeijer J, Beishuizen A, Hom HW, Blans MJ, Bosch FH, van Putten MJAM

**Objective:** Early electroencephalography measures contribute to outcome prediction of comatose patients after cardiac arrest. We present predictive values of a new cerebral recovery index, based on a combination of quantitative electroencephalography measures, extracted every hour, and combined by the use of a random forest classifier.
**Design:** Prospective observational cohort study.
**Setting:** Medical ICU of two large teaching hospitals in the Netherlands.
**Patients:** Two hundred eighty-three consecutive comatose patients after cardiac arrest.
**Interventions:** None.
**Measurements and main results:** Continuous electroencephalography was recorded during the first 3 days. Outcome at 6 months was dichotomized as good (Cerebral Performance Category 1-2, no or moderate disability) or poor (Cerebral Performance Category 3-5, severe disability, comatose, or death). Nine quantitative electroencephalography measures were extracted. Patients were randomly divided over a training and validation set. Within the training set, a random forest classifier was fitted for each hour after cardiac arrest. Diagnostic accuracy was evaluated in the validation set. The relative contributions of resuscitation parameters and patient characteristics were evaluated. The cerebral recovery index ranges from 0 (prediction of death) to 1 (prediction of full recovery). Poor outcome could be predicted at a threshold of 0.34 without false positives at a sensitivity of 56% at 12 hours after cardiac arrest. At 24 hours, sensitivity of 65% with a false positive rate of 6% was obtained. Good neurologic outcome could be predicted with sensitivities of 63% and 58% at a false positive rate of 6% and 7% at 12 and 24 hours, respectively. Adding patient characteristics was of limited additional predictive value.

**Conclusions:** A cerebral recovery index based on a combination of intermittently extracted, optimally combined quantitative electroencephalography measures provides unequalled prognostic value for comatose patients after cardiac arrest and enables bedside EEG interpretation of unexperienced readers**.**

Gepubliceerd: Crit Care Med 2017 Aug;45(8):e789-e797
Impact factor: 7.050

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**14. Predicting Outcome in Postanoxic Coma: Are Ten EEG Electrodes Enough?**
Tjepkema-Cloostermans MC, Hofmeijer J, Hom HW, Bosch FH, van Putten MJAM

**Introduction:** Increasing evidence supports that early EEG recordings reliably contribute to outcome prediction in comatose patients with postanoxic encephalopathy. As postanoxic encephalopathy typically results in generalized EEG abnormalities, spatial resolution of a small number of electrodes is likely sufficient, which will reduce set-up time. Here, the authors compare a reduced and a 21-channel EEG for outcome prediction.
**Methods:** EEG recordings from 142 prospectively collected patients with postanoxic encephalopathy were reassessed by two independent reviewers using a reduced (10 electrodes) bipolar montage. Classification and prognostic accuracy were compared with the full (21 electrodes) montage. The full montage consensus was considered Gold Standard.
**Results:** Sixty-seven patients (47%) had good outcome. The agreement between the individual reviewers using the reduced montage and the Gold Standard score was good (kappa = 0.75-0.79). The interobserver agreement was not affected by reducing the number of electrodes (kappa = 0.78 for the reduced montage vs. 0.71 for the full montage). An isoelectric, low-voltage, or burst-suppression with identical bursts pattern at 24 hours invariably predicted poor outcome in both montages, with similar prognostic accuracy. A diffusely slowed or normal EEG pattern at 12 hours was associated with good outcome in both montages.
**Conclusions:** Reducing the number of electrodes from 21 to 10 does not affect EEG classification or prognostic accuracy in patients with postanoxic coma**.**

Gepubliceerd: J Clin Neurophysiol 2017 May;34(3):207-12
Impact factor: 1.224

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**15. Diaphragm Atrophy and Weakness in the Absence of Mitochondrial Dysfunction in the Critically Ill**

van den Berg M, Hooijman PE, Beishuizen A, de Waard MC, Paul MA, Hartemink KJ, van Hees HWH, Lawlor MW, Brocca L, Bottinelli R, Pellegrino MA, Stienen GJM, Heunks LMA, Wust RCI, Ottenheijm CAC

**Rationale:** The clinical significance of diaphragm weakness in critically ill patients is evident: it prolongs ventilator dependency and increases morbidity, duration of hospital stay, and health care costs. The mechanisms underlying diaphragm weakness are unknown, but might include mitochondrial dysfunction and oxidative stress.
**Objectives:** We hypothesized that weakness of diaphragm muscle fibers in critically ill patients is accompanied by impaired mitochondrial function and structure, and by increased markers of oxidative stress.
**Methods:** To test these hypotheses, we studied contractile force, mitochondrial function, and mitochondrial structure in diaphragm muscle fibers. Fibers were isolated from diaphragm biopsies of 36 mechanically ventilated critically ill patients and compared with those isolated from biopsies of 27 patients with suspected early-stage lung malignancy (control subjects).
**Measurements and main results:** Diaphragm muscle fibers from critically ill patients displayed significant atrophy and contractile weakness, but lacked impaired mitochondrial respiration and increased levels of oxidative stress markers. Mitochondrial energy status and morphology were not altered, despite a lower content of fusion proteins.
**Conclusions:** Critically ill patients have manifest diaphragm muscle fiber atrophy and weakness in the absence of mitochondrial dysfunction and oxidative stress. Thus, mitochondrial dysfunction and oxidative stress do not play a causative role in the development of atrophy and contractile weakness of the diaphragm in critically ill patients**.**

Gepubliceerd: Am J Respir Crit Care Med 2017 Dec 15;196(12):1544-58
Impact factor: 13.204

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**16. Low caspofungin exposure in patients in the Intensive Care Unit**
van der Elst KC, Veringa A, Zijlstra JG, Beishuizen A, Klont R, Brummelhuis-Visser P, Uges DR, Touw DJ, Kosterink JG, van der Werf TS, Alffenaar JC

In critically ill patients, drug exposure may be influenced by altered drug distribution and clearance. Earlier studies showed that the variability in caspofungin exposure was high in Intensive Care Unit (ICU) patients. The primary objective of this study was to determine if the standard dose of caspofungin resulted in adequate exposure in critically ill patients. A multicenter prospective study in ICU patients with

(suspected) invasive candidiasis was conducted in the Netherlands, from November 2013 to October 2015. Patients received standard caspofungin treatment and the exposure was determined on day 3 of treatment. An area under the concentration-time curve over 24 hours (AUC0-24h) of 98 mg*h/L was considered adequate exposure. In case of low exposure (i.e. <79 mg*h/L; >/=20% lower AUC0-24h), the caspofungin dose was increased and the exposure re-evaluated. Twenty patients were included in the study, of which 5 had a positive blood culture. The median caspofungin AUC0-24h at day 3 was 78 mg*h/L (interquartile range (IQR), 69 - 97 mg*h/L). A low AUC0-24h (<79 mg*h/L) was seen in 10 patients. The AUC0-24h was significantly and positively correlated with the caspofungin dose in mg/kg/day (P = 0.011). The median AUC0-24h with a caspofungin dose of 1 mg/kg was estimated using a pharmacokinetic model and was 114.9 mg*h/L (IQR, 103.2 - 143.5 mg*h/L). In conclusion, the caspofungin exposure in ICU patients in this study was low compared with healthy volunteers and other (non-)critically ill patients, most likely due to a larger volume of distribution. A weight-based dose regimen is probably more suitable for patients with substantially altered drug distribution**.**

Gepubliceerd: Antimicrob Agents Chemother 2017;61(2):e01582-16
Impact factor: 4.302

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**17. Functional outcome after surgery in patients with bone sarcoma around the knee; results from a long-term prospective study**
van Egmond-van Dam JC, Bekkering WP, Bramer JAM, Beishuizen A, Fiocco M, Dijkstra PDS

**Background and objectives:** In a previous conducted study functional outcome of young patients with bone sarcoma located around the knee was longitudinally evaluated during the first 2 years postoperatively. Functional outcome improved significantly over the first 2 years. The purpose of this descriptive study was to evaluate the functional outcome of these patients at long-term follow-up of 7 years.
**Methods:** Functional outcome was assessed with the TESS, MSTS, Baecke questionnaire, and three functional performance tests: time up and down stairs (TUDS), various walking activities (VWA), and the 6-min walking test (6MWT). Linear Mixed Model has been employed for the repeated measurements.
**Results:** Twenty patients of the original study (n = 44) participated in the current study. Fifteen limb-salvage and five ablative surgery patients, median follow-up 7.4 years (6.8-8.0) (CI 95%), mean age 22.3 years (18.2-31.6). Between 2 and 7 years after surgery, 8 limb-salvage patients (53%) encountered surgery related complications. Questionnaires and functional performance tests showed no significant

difference in functional outcome between 2 years and 7 years after surgery (P < 0.05).
**Conclusions:** Between 2 years and follow-up at average 7 years after surgery no further improvements were noticed at young patients with a bone sarcoma located around the knee**.**

Gepubliceerd: J Surg Oncol 2017 Jun;115(8):1028-32
Impact factor: 2.993

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**18. Is a Single Initial Procalcitonin Test Sufficient in Septic, Critically Ill Patients to Minimize Antibiotic Use?**
van Oers JAH, de Jong E, Beishuizen AB, Nijsten MW, Girbes AR, de Lange DW

Gepubliceerd: Chest 2017 Jul;152(1):218-9
Impact factor: 6.147

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**19. Management of Respiratory Infections with Use of Procalcitonin: Moving toward More Personalized Antibiotic Treatment Decisions**
Wirz Y, Branche A, Wolff M, Welte T, Nobre V, Reinhart K, Falsey AR, Damas P, Beishuizen A, Deliberato RO, Shehabi Y, Jensen JS, Mueller B, Schuetz P

Due to overlap of clinical findings and low sensitivity of bacterial diagnostic tests, differentiation between bacterial and viral respiratory tract infections remains challenging, ultimately leading to antibiotic overuse in this population of patients. Addition of procalcitonin, a blood biomarker expressed by epithelial cells in response to bacterial infections, to the clinical assessment leads to a reduction in inappropriate antibiotic initiation. Procalcitonin also provides prognostic information about the resolution of illness, and significant decreases over time are a strong signal for the discontinuation of antibiotics. Current evidence from randomized trials indicates that procalcitonin-guided antibiotic stewardship results in a reduction in antibiotic use and antibiotic side effects, which importantly translates into improved survival of patients with respiratory infections. Inclusion of procalcitonin into antibiotic stewardship algorithms thus improves the diagnostic and therapeutic management of patients presenting with respiratory illnesses and holds great promise to mitigate the global bacterial resistance crisis**.**

Gepubliceerd: ACS Infect Dis 2017 Dec 8;3(12):875-9
Impact factor: 3.600

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**20. Determination of the feasibility of a multicomponent intervention program to prevent delirium in the Intensive Care Unit: A modified RAND Delphi study**
Wassenaar A, van den Boogaard M, Underpin-Icu Study Group, incl. Beishuizen A, Schoonhoven L, Pickkers P

**Background:** Delirium is common in Intensive Care Unit (ICU) patients and associated with poor outcome. In non-ICU patients a multicomponent intervention program with non-pharmacological interventions has shown to reduce delirium. Currently, there is insufficient evidence regarding the effects of such a program in ICU patients. We developed a draft program based on a review. As most studies were conducted in non-ICU patients, the feasibility of the program in ICU patients needs to be assessed before investigating its effectiveness.
**Objectives:** To determine experts' opinion and to achieve group consensus on the feasibility and completeness of the multicomponent intervention program for ICU patients.
**Methods:** A modified RAND/UCLA Appropriateness Method Delphi study was used. A total of 38 experts were selected following purposive sampling. Round one informed the experts about the draft program and asked for their opinion about its feasibility and completeness. In round two the experts were asked to reconsider their opinion based on changes made, and to rank the interventions in order of importance. The feasibility was scored using a 9-point Likert scale. A disagreement index (DI) and panel median were calculated to determine the level of agreement.
**Results:** During Delphi round one 100% of the questionnaires was completed, during round two 79%. After two rounds the experts agreed on the feasibility of the interventions targeting sleep deprivation (panel median 7.00, DI 0.26), immobility (panel median 8.00, DI 0.22), visual and hearing impairment (panel median 8.00, DI 0.19), and cognitive impairment (panel median 8.00, DI 0.23), except for cognitive training (panel median 5.00, DI 0.52).
**Conclusions:** During this study a feasible multicomponent intervention program to prevent ICU delirium was developed based on expert consensus. As no consensus was reached on cognitive training, a pilot study is planned to determine the feasibility of cognitive training in the ICU.

Gepubliceerd in: Aust Crit Care 2017 Nov;30(6):321-7
Impact factor: 1.907

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Totale impact factor: 95.555
Gemiddelde impact factor: 4.778

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

# Interne Geneeskunde

**1. Implementation of erythroid lineage analysis by flow cytometry in diagnostic models for myelodysplastic syndromes**
Cremers EM, Westers TM, Alhan C, Cali C, Visser-Wisselaar HA, Chitu DA, van der Velden VH, Te Marvelde JG, Klein SK, Muus P, Vellenga E, De Greef GE, Legdeur MC, Wijermans PW, Stevens-Kroef MJ, da Silva-Coelho P, Jansen JH, Ossenkoppele GJ, van de Loosdrecht AA

Flow cytometric analysis is a recommended tool in the diagnosis of myelodysplastic syndromes. Current flow cytometric approaches evaluate the (im)mature myelo-/monocytic lineage with a median sensitivity and specificity of ~71% and ~93%. We hypothesized that addition of erythroid lineage analysis could increase the sensitivity of flow cytometry. Hereto, we validated the analysis of erythroid lineage parameters recommended by the International/European LeukemiaNet Working Group for Flow Cytometry in Myelodysplastic Syndromes and incorporated this evaluation in currently applied flow cytometric models. One hundred and sixty-seven bone marrow aspirates were analyzed, 106 patients with myelodysplastic syndromes and 61 cytopenic controls. There was a strong correlation between presence of erythroid aberrancies assessed by flow cytometry and the diagnosis myelodysplastic syndromes, validating the previously described erythroid evaluation. Furthermore, addition of erythroid aberrancies to two different flow cytometric models led to an increased sensitivity to detect myelodysplastic syndromes: from 74% to 86% for the addition to the diagnostic score designed by Ogata and colleagues, and from 69% to 80% for the addition to the integrated flow cytometric score for myelodysplastic syndromes, designed by our group. In both models the specificity was unaffected. The high sensitivity and specificity of flow cytometry in the detection of myelodysplastic syndromes illustrates the important value of flow cytometry in a standardized diagnostic approach. The trial is registered at www.trialregister.nl as NTR1825; EudraCT nr.: 2008-002195-10**.**

Gepubliceerd: Haematologica 2017;102(2):320-6
Impact factor: 7.702

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**2. Successful Transfer of Umbilical Cord Blood CD34+ Hematopoietic Stem and Progenitor-derived NK Cells in Older Acute Myeloid Leukemia Patients**
Dolstra H, Roeven MWH, Spanholtz J, Hangalapura BN, Tordoir M, Maas F, Leenders M, Bohme F, Kok N, Trilsbeek C, Paardekooper J, van der Waart AB, Westerweel PE, Snijders TJF, Cornelissen J, Bos G, Pruijt HFM, de Graaf AO, van

der Reijden BA, Jansen JH, van der Meer A, Huls G, Cany J, Preijers F, Blijlevens NMA, Schaap NM

**Purpose:** Older acute myeloid leukemia (AML) patients have a poor prognosis; therefore, novel therapies are needed. Allogeneic natural killer (NK) cells have been adoptively transferred with promising clinical results. Here, we report the first-in-human study exploiting a unique scalable NK-cell product generated ex vivo from CD34+ hematopoietic stem and progenitor cells (HSPC) from partially HLA-matched umbilical cord blood units.Experimental
**Design:** Ten older AML patients in morphologic complete remission received an escalating HSPC-NK cell dose (between 3 and 30 x 106/kg body weight) after lymphodepleting chemotherapy without cytokine boosting.
**Results:** HSPC-NK cell products contained a median of 75% highly activated NK cells, with <1 x 104 T cells/kg and <3 x 105 B cells/kg body weight. HSPC-NK cells were well tolerated, and neither graft-versus-host disease nor toxicity was observed. Despite no cytokine boosting being given, transient HSPC-NK cell persistence was clearly found in peripheral blood up to 21% until day 8, which was accompanied by augmented IL15 plasma levels. Moreover, donor chimerism up to 3.5% was found in bone marrow. Interestingly, in vivo HSPC-NK cell maturation was observed, indicated by the rapid acquisition of CD16 and KIR expression, while expression of most activating receptors was sustained. Notably, 2 of 4 patients with minimal residual disease (MRD) in bone marrow before infusion became MRD negative (<0.1%), which lasted for 6 months.
**Conclusions:** These findings indicate that HSPC-NK cell adoptive transfer is a promising, potential "off-the-shelf" translational immunotherapy approach in AML. Clin Cancer Res; 23(15); 4107-18. (c)2017 AACR**.**

Gepubliceerd: Clin Cancer Res 2017 Aug 1;23(15):4107-18
Impact factor: 9.619

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**3. Treatment of secondary central nervous system lymphoma with intrathecal rituximab, high-dose methotrexate, and R-DHAP followed by autologous stem cell transplantation: results of the HOVON 80 phase 2 study**
Doorduijn JK, van Imhoff GW, van der Holt B, Schouten HC, Schaafsma MR, MacKenzie MA, Baars JW, Kersten MJ, Lugtenburg PJ, van den Bent MJ, Enting RH, Spoelstra FM, Poortmans P, Bromberg JEC

The prognosis of central nervous system (CNS) relapse of systemic non-Hodgkin lymphoma is poor with 1-year survival historically at 0% to 20%. Aiming to improve these results, we performed a multicenter phase 2 study in patients with a CNS

relapse, with or without concurrent systemic relapse. Treatment consisted of 2 cycles of R-DHAP alternating with high-dose methotrexate (MTX) and was combined with intrathecal rituximab. Responding patients received a third R-DHAP-MTX cycle followed by busulfan and cyclophosphamide myeloablative therapy and autologous stem cell transplantation. In patients with persistent cerebrospinal fluid lymphoma after cycle 1, the intrathecal rituximab was replaced by intrathecal triple therapy, with MTX, cytarabine, and dexamethasone. Thirty-six patients were included. Eighteen had evidence of cerebrospinal fluid lymphoma, 24 had brain parenchymal disease, and 20 (56%) had concurrent systemic disease. The overall response rate after 2 R-DHAP-MTX was 53% (19/36), with 22% (8/36) complete remission. Fifteen patients (42%) underwent a transplant. One-year progression-free survival was 19% (95% confidence interval, 9-34): 25% in patients without and 15% in patients with systemic disease. One-year overall survival was 25% (95% confidence interval, 12-40). This treatment regimen did not result in a major improvement of outcome of secondary CNS lymphoma, especially when concurrent systemic disease was present. Registered in the Dutch trial register www.trialregister.nl, NTR1757; EudraCT number 2006-002141-37.

Gepubliceerd: Hematol Oncol 2017 Dec;35(4):497-503
Impact factor: 3.118

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**4. Prevalence by Computed Tomographic Angiography of Coronary Plaques in South Asian and White Patients With Type 2 Diabetes Mellitus at Low and High Risk Using Four Cardiovascular Risk Scores (UKPDS, FRS, ASCVD, and JBS3)**
Gobardhan SN, Dimitriu-Leen AC, van Rosendael AR, van Zwet EW, Roos CJ, Oemrawsingh PV, Kharagjitsingh AV, Jukema JW, Delgado V, Schalij MJ, Bax JJ, Scholte AJ

The aim of this study was to explore the association between various cardiovascular (CV) risk scores and coronary atherosclerotic burden on coronary computed tomography angiography (CTA) in South Asians with type 2 diabetes mellitus and matched whites. Asymptomatic type 2 diabetic South Asians and whites were matched for age, gender, body mass index, hypertension, and hypercholesterolemia. Ten-year CV risk was estimated using different risk scores (United Kingdom Prospective Diabetes Study [UKPDS], Framingham Risk Score [FRS], AtheroSclerotic CardioVascular Disease [ASCVD], and Joint British Societies for the prevention of CVD [JBS3]) and categorized into low- and high-risk groups. The presence of coronary artery calcium (CAC) and obstructive coronary artery disease (CAD; >/=50% stenosis) was assessed using coronary CTA. Finally, the relation between coronary atherosclerosis on CTA and the low- and high-risk groups was

compared. UKPDS, FRS, and ASCVD showed no differences in estimated CV risk between 159 South Asians and 159 matched whites. JBS3 showed a significant greater absolute CV risk in South Asians (18.4% vs 14.2%, p <0.01). Higher presence of CAC score >0 (69% vs 55%, p <0.05) and obstructive CAD (39% vs 27%, p <0.05) was observed in South Asians. South Asians categorized as high risk, using UKPDS, FRS, and ASCVD, showed more CAC and CAD compared than whites. JBS3 showed no differences. In conclusion, asymptomatic South Asians with type 2 diabetes mellitus more frequently showed CAC and obstructive CAD than matched whites in the population categorized as high-risk patients using UKPDS, FRS, and ASCVD as risk estimators. However, JBS3 seems to correlate best to CAC and CAD in both ethnicity groups compared with the other risk scores.

Gepubliceerd: Am J Cardiol 2017;119(5):705-11
Impact factor: 3.398

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**5. Dutch Melanoma Treatment Registry: Quality assurance in the care of patients with metastatic melanoma in the Netherlands**

Jochems A, Schouwenburg MG, Leeneman B, Franken MG, van den Eertwegh AJ, Haanen JB, Gelderblom H, Uyl-de Groot CA, Aarts MJ, van den Berkmortel FW, Blokx WA, Cardous-Ubbink MC, Groenewegen G, de Groot JW, Hospers GA, Kapiteijn E, Koornstra RH, Kruit WH, Louwman MW, Piersma D, van Rijn RS, Ten Tije AJ, Vreugdenhil G, Wouters MW, van der Hoeven JJ

**Background:** In recent years, the treatment of metastatic melanoma has changed dramatically due to the development of immune checkpoint and mitogen-activated protein (MAP) kinase inhibitors. A population-based registry, the Dutch Melanoma Treatment Registry (DMTR), was set up in July 2013 to assure the safety and quality of melanoma care in the Netherlands. This article describes the design and objectives of the DMTR and presents some results of the first 2 years of registration.
**Methods:** The DMTR documents detailed information on all Dutch patients with unresectable stage IIIc or IV melanoma. This includes tumour and patient characteristics, treatment patterns, clinical outcomes, quality of life, healthcare utilisation, informal care and productivity losses. These data are used for clinical auditing, increasing the transparency of melanoma care, providing insights into real-world cost-effectiveness and creating a platform for research.
**Results:** Within 1 year, all melanoma centres were participating in the DMTR. The quality performance indicators demonstrated that the BRAF inhibitors and ipilimumab have been safely introduced in the Netherlands with toxicity rates that were consistent with the phase III trials conducted. The median overall survival of patients treated with

systemic therapy was 10.1 months (95% confidence interval [CI] 9.1-11.1) in the first registration year and 12.7 months (95% CI 11.6-13.7) in the second year.
**Conclusion:** The DMTR is the first comprehensive multipurpose nationwide registry and its collaboration with all stakeholders involved in melanoma care reflects an integrative view of cancer management. In future, the DMTR will provide insights into challenging questions regarding the definition of possible subsets of patients who benefit most from the new drugs**.**

Gepubliceerd: Eur J Cancer 2017 Feb;72:156-65
Impact factor: 6.029

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**6. Genomic array as compared to karyotyping in myelodysplastic syndromes in a prospective clinical trial**
Stevens-Kroef MJ, Olde WD, Elldrissi-Zaynoun N, van der Reijden B, Cremers EMP, Alhan C, Westers TM, Visser-Wisselaar HA, Chitu DA, Cunha SM, Vellenga E, Klein SK, Wijermans P, De Greef GE, Schaafsma MR, Muus P, Ossenkoppele GJ, van de Loosdrecht AA, Jansen JH

Karyotyping is considered as the gold standard in the genetic subclassification of myelodysplastic syndrome (MDS). Oligo/SNP-based genomic array profiling is a high-resolution tool that also enables genome wide analysis. We compared karyotyping with oligo/SNP-based array profiling in 104 MDS patients from the HOVON-89 study. Oligo/SNP-array identified all cytogenetically defined genomic lesions, except for subclones in two cases and balanced translocations in three cases. Conversely, oligo/SNP-based genomic array profiling had a higher success rate, showing 55 abnormal cases, while an abnormal karyotype was found in only 35 patients. In nine patients whose karyotyping was unsuccessful because of insufficient metaphases or failure, oligo/SNP-based array analysis was successful. Based on cytogenetic visible abnormalities as identified by oligo/SNP-based genomic array prognostic scores based on IPSS/-R were assigned. These prognostic scores were identical to the IPSS/-R scores as obtained with karyotyping in 95%-96% of the patients. In addition to the detection of cytogenetically defined lesions, oligo/SNP-based genomic profiling identified focal copy number abnormalities or regions of copy neutral loss of heterozygosity that were out of the scope of karyotyping and fluorescence in situ hybridization. Of interest, in 26 patients we demonstrated such cytogenetic invisible abnormalities. These abnormalities often involved regions that are recurrently affected in hematological malignancies, and may therefore be of clinical relevance. Our findings indicate that oligo/SNP-based genomic array can be used to identify the vast majority of recurrent cytogenetic abnormalities in MDS. Furthermore, oligo/SNP-

based array profiling yields additional genetic abnormalities that may be of clinical importance**.**

Gepubliceerd: Genes Chromosomes Cancer 2017 Jul;56(7):524-34
Impact factor: 3.696

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**7. Comparative value of post-remission treatment in cytogenetically normal AML subclassified by NPM1 and FLT3-ITD allelic ratio**
Versluis J, In 't Hout FE, Devillier R, van Putten WL, Manz MG, Vekemans MC, Legdeur MC, Passweg JR, Maertens J, Kuball J, Biemond BJ, Valk PJ, van der Reijden BA, Meloni G, Schouten HC, Vellenga E, Pabst T, Willemze R, Lowenberg B, Ossenkoppele G, Baron F, Huls G, Cornelissen JJ

Post-remission treatment (PRT) in patients with cytogenetically normal (CN) acute myeloid leukemia (AML) in first complete remission (CR1) is debated. We studied 521 patients with CN-AML in CR1, for whom mutational status of NPM1 and FLT3-ITD was available, including the FLT3-ITD allelic ratio. PRT consisted of reduced intensity conditioning (RIC) allogeneic hematopoietic stem cell transplantation (alloHSCT) (n=68), myeloablative conditioning (MAC) alloHSCT (n=137), autologous hematopoietic stem cell transplantation (autoHSCT) (n=168) or chemotherapy (n=148). Favorable overall survival (OS) was found for patients with mutated NPM1 without FLT3-ITD (71+/-4%). Outcome in patients with a high FLT3-ITD allelic ratio appeared to be very poor with OS and relapse-free survival (RFS) of 23+/-8% and 12+/-6%, respectively. Patients with wild-type NPM1 without FLT3-ITD or with a low allelic burden of FLT3-ITD were considered as intermediate-risk group because of similar OS and RFS at 5 years, in which PRT by RIC alloHSCT resulted in better OS and RFS as compared with chemotherapy (hazard ratio (HR) 0.56, P=0.022 and HR 0.50, P=0.004, respectively) or autoHSCT (HR 0.60, P=0.046 and HR 0.60, P=0.043, respectively). The lowest cumulative incidence of relapse (23+/-4%) was observed following MAC alloHSCT. These results suggest that alloHSCT may be preferred in patients with molecularly intermediate-risk CN-AML, while the choice of conditioning type may be personalized according to risk for non-relapse mortality.Leukemia advance online publication, 15 July 2016; doi:10.1038/leu.2016.183**.**

Gepubliceerd: Leukemia 2017;31(1):26-33
Impact factor: 11.702

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**8. Oncology is not waiting for "shared decision-making" Patients and doctors generally reach consensus**

Wymenga AN

In recent times, the importance of shared decision-making (SDM) when making medical decisions has been emphasised. In general, SDM is seen as a consultative communication style, mainly used in reaching important, preference-sensitive decisions when multiple options are available, each with advantages and disadvantages. SDM is particularly advocated in palliative cancer treatments, as patients have different goals for treatment and different trade-offs for side effects. Decision-support tools might facilitate the process of SDM, but might also fill a needs' gap only in a minority of patients. As cancer treatment increasingly becomes more personalised, cancer patients also deserve personalised guidance; sometimes this means sharing decision-making but sometimes paternalistic advice is actually required. It is questionable whether general decision-making tools will have significant impact on patient satisfaction in medical decision-making**.**

Gepubliceerd: Ned Tijdschr Geneeskd 2017;161:D1393
Impact factor: 0

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**9. Therapeutic value of clofarabine in younger and middle-aged (18-65 years) adults with newly diagnosed AML**
Lowenberg B, Pabst T, Maertens J, van Norden Y, Biemond BJ, Schouten HC, Spertini O, Vellenga E, Graux C, Havelange V, De Greef GE, de Weerdt O, Legdeur MJ, Kuball J, Kooy MV, Gjertsen BT, Jongen-Lavrencic M, van de Loosdrecht AA, van Lammeren-Venema D, Hodossy B, Breems DA, Chalandon Y, Passweg J, Valk PJ, Manz MG, Ossenkoppele GJ

Clofarabine has demonstrated antileukemic activity in acute myeloid leukemia (AML) but has yet to be critically evaluated in younger adults in the frontline with standard chemotherapy. We compared 2 induction regimens in newly diagnosed patients ages 18 to 65 with acute myeloid leukemia (AML)/high-risk myelodysplastic syndromes, that is, idarubicine-cytarabine (cycle I) and amsacrine-cytarabine (cycle II) without or with clofarabine (10 mg/m(2) on days 1-5 of each of both cycles). Consolidation involved chemotherapy with or without hematopoietic stem cell transplantation. Event-free survival (EFS, primary endpoint) and other clinical endpoints and toxicities were assessed. We randomized 402 and 393 evaluable patients to the control or clofarabine induction treatment arms. Complete remission rates (89%) did not differ but were attained faster with clofarabine (66% vs 75% after cycle I). Clofarabine added grades 3 to 4 toxicities and delayed hematological recovery. At a median follow-up of 36 months, the study reveals no differences in overall survival and EFS between the control (EFS, 35% +/- 3 [standard error] at 4 years) and clofarabine

treatments (38% +/- 3) but a markedly reduced relapse rate (44% +/- 3 vs 35% +/- 3) in favor of clofarabine and an increased death probability in remission (15% +/- 2 vs 22% +/- 3). In the subgroup analyses, clofarabine improved overall survival and EFS for European Leukemia Net (ELN) 2010 intermediate I prognostic risk AML (EFS, 26% +/- 4 vs 40% +/- 5 at 4 years; Cox P = .002) and for the intermediate risk genotype NPM1 wild-type/FLT3 without internal-tandem duplications (EFS, 18% +/- 5 vs 40% +/- 7; Cox P < .001). Clofarabine improves survival in subsets of intermediate-risk AML only. HOVON-102 study is registered at Netherlands Trial Registry #NTR2187.

Gepubliceerd in: Blood 2017 Mar 23;129(12):1636-45
Impact factor: 13.164

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**10. Effectiveness of Long-term Doxycycline Treatment and Cognitive-Behavioral Therapy on Fatigue Severity in Patients with Q Fever Fatigue Syndrome (Qure Study): A Randomized Controlled Trial**

Keijmel SP, Delsing CE, Bleijenberg G, van der Meer JWM, Donders RT, Leclercq M, Kampschreur LM, van den Berg M, Sprong T, Nabuurs-Franssen MH, Knoop H, Bleeker-Rovers CP

**Background:** Approximately 20% of patients with acute Q fever will develop chronic fatigue, referred to as Q fever fatigue syndrome (QFS). The objective of this randomized controlled clinical trial was to assess the efficacy of either long-term treatment with doxycycline or cognitive-behavioral therapy (CBT) in reducing fatigue severity in patients with QFS.
**Methods:** Adult patients were included who met the QFS criteria according to the Dutch guideline: a new onset of severe fatigue lasting >/=6 months with significant disabilities, related to an acute Q fever infection, without other somatic or psychiatric comorbidity explaining the fatigue. Using block randomization, patients were randomized between oral study medication and CBT (2:1) for 24 weeks. Second, a double-blind randomization between doxycycline (200 mg/day, once daily) and placebo was performed in the medication group. Primary outcome was fatigue severity at end of treatment (EOT; week 26), assessed with the Checklist Individual Strength subscale Fatigue Severity.
**Results:** Of 155 patients randomized, 154 were included in the intention-to-treat analysis (doxycycline, 52; placebo, 52; CBT, 50). At EOT, fatigue severity was similar between doxycycline (40.8 [95% confidence interval {CI}, 37.3-44.3]) and placebo (37.8 [95% CI, 34.3-41.2]; difference, doxycycline vs placebo, -3.0 [97.5% CI, -8.7 to 2.6]; P = .45). Fatigue severity was significantly lower after CBT (31.6 [95% CI, 28.0-

35.1]) than after placebo (difference, CBT vs placebo, 6.2 [97.5% CI, .5-11.9]; P = .03).
**Conclusions:** CBT is effective in reducing fatigue severity in QFS patients. Long-term treatment with doxycycline does not reduce fatigue severity in QFS patients compared to placebo.
**Clinical Trials Registration:** NCT01318356.

Gepubliceerd in: Clin Infect Dis 2017 Apr 15;64(8):998-1005
Impact factor: 8.216

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**11. A woman with fever and a rash**
Ros MM, Delsing CE

A 55-year-old woman with fever, a rash and elevated liver enzymes was diagnosed with drug reaction with eosinophilia and systemic symptoms (DRESS). After treatment with high-dose prednisolone and withholding carbamazepine, all symptoms resolved completely. This case emphasises the importance of recognizing a drug-related cause of fever and rash other than infectious causes.

Gepubliceerd in: Ned Tijdschr Geneeskd 2017;161(0):D1118
Impact factor: 0

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Totale impact factor: 66.644
Gemiddelde impact factor: 6.059

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 8.216
Gemiddelde impact factor: 2.739

# Kindergeneeskunde

**1. The early postnatal nutritional intake of preterm infants affected neurodevelopmental outcomes differently in boys and girls at 24 months**
Christmann V, Roeleveld N, Visser R, Janssen AJ, Reuser JJ, van Goudoever JB, van Heijst AF

**Aim:** This study assessed whether increased amino acid and energy intake in preterm infants during the first week of life was associated with improved neurodevelopment at the corrected age (CA) of 24 months.
**Methods:** We evaluated preterm infants from two consecutive cohorts in 2004 (Cohort 1) and 2005 (Cohort 2) with different nutritional intakes in the Netherlands. Nutritional intake and growth were recorded until week 5 and after discharge. Neurodevelopment was determined using the Bayley Scales of Infant Development - Second Edition at a CA of 24 months.
**Results:** Compared to Cohort 1 (n = 56), Cohort 2 (n = 56) received higher nutritional intake during week 1 ($p < 0.001$). The weight gain in Cohort 2 was higher until week 5, especially among boys ($p < 0.002$). The mean Mental Developmental Index (MDI) scores did not differ, but Cohort 2 was associated with an increased chance of having an MDI >/= 85, with an odds ratio of 6.4 and 95% confidence interval (CI) of 1.5-27.4, among all girls with a higher protein intake (5.3, 1.2-23.3). The Psychomotor Developmental Index increased with increasing nutritional intake, especially among boys (beta-coefficient 3.1, 95% CI 0.2-6.0).
**Conclusion:** Higher nutritional intake was associated with different improvements in growth and neurodevelopment in boys and girls**.**

Gepubliceerd: Acta Paediatr 2017;106(2):242-9
Impact factor: 2.043

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**2. Concerns with beta2-agonists in pediatric asthma - a clinical perspective**
Kersten ET, Koppelman GH, Thio BJ

Beta2-adrenoreceptor agonists (beta2-agonists) are extensively used in the treatment of childhood asthma. However, there have been concerns regarding their adverse effects and safety. In 2005, the FDA commissioned a "Black Box Warning" communicating the potential for an increased risk for serious asthma exacerbations or asthma related deaths, with the regular use of LABAs. In a meta-analysis of controlled clinical trials, the incidence of severe adverse events appeared to be highest in the 4-11 year age group. Several mechanisms have been proposed

regarding the risk of regular use of beta2-agonists, such as masking patients' perception of worsening asthma, desensitization and downregulation of the beta2-adrenoreceptor, pro-inflammatory effects of beta2-agonists, pharmacogenetic effects of beta2-adrenoreceptor polymorphisms and age related differences in pathophysiology of asthma. In this paper, we review beta2-receptor pharmacology, discuss the concerns regarding treatment with beta2-agonists in childhood asthma, and provide suggestions for clinical pediatric practice in the light of current literature.

Gepubliceerd: Paediatr Respir Rev 2017;21:80-5
Impact factor: 2.214

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**3. Instruments to measure anxiety in children, adolescents, and young adults with cancer: a systematic review**
Lazor T, Tigelaar L, Pole JD, De Souza C, Tomlinson D, Sung L

**Purpose:** The primary objective was to describe anxiety measurement instruments used in children and adolescents with cancer or undergoing hematopoietic stem cell transplantation (HSCT) and summarize their content and psychometric properties.
**Methods:** We conducted searches of MEDLINE, Embase, PsycINFO, HAPI, and CINAHL. We included studies that used at least one instrument to measure anxiety quantitatively in children or adolescents with cancer or undergoing HSCT. Two authors independently identified studies and abstracted study demographics and instrument characteristics.
**Results:** Twenty-seven instruments, 14 multi-item and 13 single-item, were used between 78 studies. The most commonly used instrument was the State-Trait Anxiety Inventory in 46 studies. Three multi-item instruments (Children's Manifest Anxiety Scale-Mandarin version, PROMIS Pediatric Anxiety Short Form, and the State-Trait Anxiety Inventory) and two single-item instruments (Faces Pain Scale-Revised and 10-cm Visual Analogue Scale, both adapted for anxiety) were found to be reliable and valid in children with cancer.
**Conclusions:** We identified 14 different multi-item and 13 different single-item anxiety measurement instruments that have been used in pediatric cancer or HSCT. Only three multi-item and two single-item instruments were identified as being reliable and valid among pediatric cancer or HSCT patients and would therefore be appropriate to measure anxiety in this population.

Gepubliceerd: Support Care Cancer 2017 Sep;25(9):2921-31
Impact factor: 2.698

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**4. BMI predicts exercise induced bronchoconstriction in asthmatic boys**
van Veen WJ, Driessen JMM, Kersten ETG, van Leeuwen JC, Brusse-Keizer MGJ, van Aalderen WMC, Thio BJ

**Background:** Exercise induced bronchoconstriction (EIB) is a frustrating morbidity of asthma in children. Obesity has been associated with asthma and with more severe EIB in asthmatic children.
**Objectives:** To quantify the effect of BMI on the risk of the occurrence of EIB in children with asthma.
**Methods:** Data were collected from six studies in which exercise challenge tests were performed according to international guidelines. We included 212 Children aged 7-18 years, with a pediatrician-diagnosed mild-to-moderate asthma.
**Results:** A total of 103 of 212 children (49%) had a positive exercise challenge (fall of FEV1 >/= 13%). The severity of EIB, as measured by the maximum fall in FEV1 , was significantly greater in overweight and obese children compared to normal weight children (respectively 23.9% vs 17.9%; P = 0.045). Asthmatic children with a BMI z-score around +1 had a 2.9-fold higher risk of the prevalence of EIB compared to children with a BMI z-score around the mean (OR 2.9; 95%CI: 1.3-6.1; P < 0.01). An increase in BMI z-score of 0.1 in boys led to a 1.4-fold increased risk of EIB (OR 1.4; 95%CI: 1.0-1.9; P = 0.03). A reduction in pre-exercise FEV1 was associated with a higher risk of EIB (last quartile six times higher risk compared to highest quartile (OR 6.1 [95%CI 2.5-14.5]).
**Conclusions:** The severity of EIB is significantly greater in children with overweight and obesity compared to non-overweight asthmatic children. Furthermore, this study shows that the BMI-z-score, even with a normal weight, is strongly associated with the incidence of EIB in asthmatic boys**.**

Gepubliceerd: Pediatr Pulmonol 2017 Sep;52(9):1130-4
Impact factor: 2.758

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**5. Application of Population Pharmacokinetic Modeling for Individualized Infliximab Dosing Strategies in Crohn Disease**
Frymoyer A, Hoekman DR, Piester TL, de Meij TG, Hummel TZ, Benninga MA, Kindermann A, Park KT

**Objectives:** The pharmacokinetics of infliximab (IFX) is highly variable in children with Crohn disease (CD), and a one-size-fits-all approach to dosing is inadequate. Model-based drug dosing can help individualize dosing strategies. We evaluated the predictive performance and clinical utility of a published population pharmacokinetic model of IFX in children with CD.

**Methods:** Within a cohort of 34 children with CD who had IFX trough concentrations measured, the pharmacokinetics of each patient was estimated in NONMEM using a published population pharmacokinetic model. Infliximab concentrations were then predicted based on each patient's dosing history and compared with actual measured concentrations (n = 59). In addition, doses 5 to 10 mg/kg and dosing intervals every 4 to 8 weeks were simulated in each patient to examine dose-trough relationships.
**Results:** Predicted concentrations were within +/-1.0 mug/mL of actual measured concentrations for 88% of measurements. The median prediction error (ie, measure of bias) was -0.15 mug/mL (95% confidence interval -0.37 to -0.05 mug/mL) and absolute prediction error (ie, measure of precision) was 0.26 mug/mL (95% confidence interval 0.15 to 0.40 mug/mL). At standard maintenance dosing of 5 mg/kg every 8 weeks, a trough >3 mug/mL was predicted to be achieved in 32% of patients. To achieve a trough >3 mug/mL, a dosing interval </=every 6 weeks was predicted to be required in 29% of patients.
**Conclusions:** A published IFX population pharmacokinetic model demonstrated accurate predictive performance in a pediatric CD population. Individualized IFX dosing strategies in children with CD will be critical to consistently achieve trough concentrations associated with optimal outcomes.

Gepubliceerd in: J Pediatr Gastroenterol Nutr 2017 Dec;65(6):639-45
Impact factor: 2.799

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**6. Raised faecal calprotectin is associated with subsequent symptomatic relapse, in children and adolescents with inflammatory bowel disease in clinical remission**
Diederen K, Hoekman DR, Leek A, Wolters VM, Hummel TZ, de Meij TG, Koot BG, Tabbers MM, Benninga MA, Kindermann A

**Background:** Reliable data on inflammatory biomarkers for predicting relapse of paediatric inflammatory bowel disease (IBD) are lacking. AIM: To investigate the predictive value of faecal calprotectin (FC) and CRP for symptomatic relapse in pediatric IBD in clinical remission.
**Methods:** In this cross-sectional cohort study, patients <18 years with Crohn's disease or ulcerative colitis in clinical remission >/=3 months were included. At baseline, clinical and biochemical disease activity were assessed using the abbreviated-Pediatric Crohn's Disease Activity Index or Pediatric Ulcerative Colitis Activity Index, and FC and CRP respectively. Disease course over the subsequent 12 months was retrospectively assessed.
**Results:** In total, 114 patients (56% males; median age 14.9 years) were included. Baseline FC was higher in patients that developed symptomatic relapse [median

(IQR), relapse 370 mug/g (86-1100) vs. remission 122 mug/g (40-344), P = 0.003]. Baseline FC was predictive of symptomatic relapse within 6 months [HR per 250 mug/g (95% CI): 1.46 (1.21-1.77), P < 0.001], with good predictive accuracy (AUC: 0.82). Optimal FC cut-off was 350 mug/g, with positive and negative predictive value of 41% and 96%. Baseline CRP was higher in patients that developed symptomatic relapse [median (IQR), relapse 1.0 mug/g (0.6-5.0) vs. remission 1.0 mug/g (0.4-2.0), P = 0.033]. Baseline CRP was predictive of symptomatic relapse within 6 months from baseline [HR per 1 mg/L (95% CI): 1.10 (1.02-1.19), P = 0.011], with fair predictive accuracy (AUC: 0.72). Optimal CRP cut-off was 1.0 mg/L, with positive and negative predictive value of 21% and 94%.
**Conclusions:** Faecal calprotectin and CRP are predictive of symptomatic relapse and may be valuable in management of paediatric IBD in clinical remission.

Gepubliceerd in: Aliment Pharmacol Ther 2017 Apr;45(7):951-60
Impact factor: 7.286

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Totale impact factor: 19.798
Gemiddelde impact factor: 3.300

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 7.670
Gemiddelde impact factor: 2.557

# Klinische chemie

**1. The added value of synovial fluid centrifugation for monosodium urate and calcium pyrophosphate crystal detection**
Boumans D, Hettema ME, Vonkeman HE, Maatman RG, van de Laar MA

The aim of the study was to assess the added value of synovial fluid (SF) centrifugation for microscopic monosodium urate (MSU) and calcium pyrophosphate (CPP) crystal detection in patients with arthritis. This is a prospective observational study using SF samples from joints of patients undergoing joint arthrocentesis. Two blinded observers assessed the SF smears by polarized light microscopy for the presence of crystals before as well as after centrifugation. SF samples were collected from 98 patients with arthritis. After exclusion, 87 samples were eligible for inclusion. Of each sample, 2 smears before and after centrifugation were prepared and microscopically examined, resulting in 348 smears per observer. Observer 1 identified MSU crystals in 18.4% and CPP in 9.2% of the smears before as well as after centrifugation. No extra MSU crystal-positive smears were identified after centrifugation. However, centrifugation yielded 4 additional CPP crystal-positive smears. Observer 2 identified MSU crystals in 15.5% and CPP crystals in 6.3% of the smears before as well as after centrifugation. Centrifugation yielded 2 additional MSU crystal-positive smears and 4 CPP crystal-positive smears. Monosodium urate crystals were well recognized without centrifugation. Centrifugation of SF had limited additional value for increasing the amount of MSU-positive smears. However, CPP crystals were identified in a higher number of smears after centrifugation than before. Therefore, centrifugation may be of additional value in selected patients with suspected calcium pyrophosphate deposition disease and to a lesser extent for gout.

Gepubliceerd: Clin Rheumatol 2017 Jul;36(7):1599-605
Impact factor: 2.365

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**2. Evaluation of a POCT device for C-reactive protein, hematocrit and leukocyte differential**
de Graaf AJ, Hiemstra SW, Kemna EW, Krabbe JG

Gepubliceerd: Clin Chem Lab Med 2017 Mar 28;55(11):e251-e253
Impact factor: 3.432

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**3. A two site comparison of two point-of-care activated clotting time systems**

Kemna EW, Kuipers C, Oude Luttikhuis-Spanjer AM, Majoor S, Boudrie R, Speekenbrink RG, Hoffman R, Krabbe JG

Gepubliceerd: Clin Chem Lab Med 2017;55(1):e13-e16
Impact factor: 3.432

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**4. A multicenter effort to improve comparability of vitamin B6 assays in whole blood**
Roelofsen-de Beer RJAC, van Zelst BD, Kos S, Maatman RGHJ, de Jonge R, de Rijke YB

Gepubliceerd: Clin Chem Lab Med 2017 Jul 21;56(1):e23-e26
Impact factor: 3.432

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**5. Fibrinogen determination according to Clauss: commutability assessment of International and commercial standards and quality control samples**
van den Besselaar AMHP, van Rijn CJJ, Cobbaert CM, Reijnierse GLA, Hollestelle MJ, Niessen RWLM, Hudig F

**Background:** Many clinical laboratories use a clotting rate assay according to Clauss for the determination of fibrinogen in citrated plasma. The aim of the present study was to assess the commutability of the current International Standard for fibrinogen (coded 09/264), three commercial fibrinogen standards, and 10 freeze-dried plasma quality control samples from various sources.
**Methods:** Clotting rate assays according to Clauss were performed on three automated instruments (Sysmex CA1500, STA-Rack Evolution and ACL-Top 700), using three commercial thrombin reagents (Siemens, Stago, and Instrumentation Laboratory). Relationships between the results obtained with the three instruments were determined with 25 fresh-frozen plasma samples obtained from patients. The deviations of the assay results obtained with the freeze-dried samples were compared with the deviations obtained with the fresh-frozen samples, according to approved CLSI guideline C53A.
**Results:** Freezing and thawing had no influence on the assay results. There were significant differences in the mean assay results (fibrinogen, g/L) for the fresh-frozen plasma samples between the three automated instruments: 2.51 (STA-Rack Evolution), 2.25 (ACL-Top 700) and 2.20 (Sysmex CA1500). Similar differences were observed for several freeze-dried plasma samples. Some freeze-dried plasma samples, including the International Standard, were out of the 95% confidence interval for the relationship between STA-Rack Evolution and Sysmex CA1500.

**Conclusions:** Some freeze-dried plasmas including the international standard for fibrinogen are not commutable among automated instruments for fibrinogen clotting rate assays according to Clauss. Our results have consequences for all interested parties in the traceability chain (WHO, industry, external quality assessment schemes, clinical laboratories).

Gepubliceerd: Clin Chem Lab Med 2017 Apr 17;55(11):1761-9
Impact factor: 3.432

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**6. Endothelial function after ST-elevation myocardial infarction in patients with high levels of high-sensitivity CRP and Lp-PLA2: A substudy of the RESPONSE randomized trial**

Kandhai-Ragunath JJ, de Wagenaar B, Doelman C, van Es J, Jorstad HT, Peters RJG, Doggen CJM, von Birgelen C

**Background:** The combination of high levels of high-sensitive C-reactive protein (hs-CRP) and lipoprotein-associated phospholipase-A2 (Lp-PLA2) was recently shown to correlate with increased cardiovascular risk. Endothelial dysfunction is also known to be a risk factor for cardiovascular events. AIM: To test among patients with previous ST-elevation myocardial infarction (STEMI) the hypothesis that high levels of both hs-CRP and Lp-PLA2 may be associated with impaired endothelium-dependent vasodilatation.
**Methods:** In this substudy of the RESPONSE randomized trial, we used reactive hyperemia peripheral artery tonometry (RH-PAT) 4 to 6weeks after STEMI and primary percutaneous coronary intervention (PPCI) to non-invasively assess endothelial function (RH-PAT index <1.67 identified endothelial dysfunction). Reliable measurements of RH-PAT, hs-CRP, and Lp-PLA2 were obtained in 68 patients, who were classified as high-risk if levels of both hs-CRP and Lp-PLA2 were in the upper tertile (>/=3.84mg/L and >239mug/L, respectively).
**Results:** Patients were 57.4+/-9.7years and 53 (77.9%) were men. 11 (16%) patients were classified as high-risk and 57 (84%) as low-to-intermediate-risk. The RH-PAT index was 1.68+/-0.22 in high-risk and 1.95+/-0.63 in low-to-intermediate-risk patients (p=0.17). Endothelial dysfunction was present in 8 (72.7%) high-risk and 26 (45.6%) low-to-intermediate-risk patients (p=0.09). Framingham risk score, NT-proBNP and fibrinogen levels were higher in high-risk patients (p</=0.03).
**Conclusion:** In this population of patients with recent STEMI and PPCI, we observed between patients with high hs-CRP and Lp-PLA levels and all other patients no more than numerical differences in endothelial function that did not reach a statistical significance. Nevertheless, further research in larger study populations may be warranted.

Gepubliceerd: Cardiovasc Revasc Med 2017 Apr;18(3):202-6
Impact factor: 0

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Totale impact factor: 16.093
Gemiddelde impact factor: 2.682

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 6.864
Gemiddelde impact factor: 3.432

# Klinische farmacie

**1. Optimizing the dose in cancer patients treated with imatinib, sunitinib and pazopanib**
Lankheet NAG, Desar IME, Mulder SF, Burger DM, Kweekel DM, van Herpen CML, van der Graaf WTA, van Erp NP

**Aim:** Fixed dose oral tyrosine kinase inhibitors imatinib, sunitinib and pazopanib show a high interpatient variability in plasma exposure. A relationship between plasma exposure and treatment outcome has been established, which supports the rationale for dose optimization of these drugs. The aim of this study was to monitor how many patients reached adequate trough levels after therapeutic drug monitoring-based dose optimization in daily practice.
**Methods:** A cohort study was performed in patients treated with imatinib, sunitinib or pazopanib of whom follow-up drug levels were measured between August 2012 and April 2016. Patients' characteristics were collected by reviewing electronic patient records. Drug levels were measured using high-performance liquid chromatography coupled with tandem mass spectrometry and trough levels were estimated using a predefined algorithm. Dose interventions were proposed based on trough levels.
**Results:** In total, 396 trough levels were determined in 109 patients. Median sample frequency per patient was 3. During the first measurement only 38% of patients showed trough levels within the predefined target ranges despite standard dosing; 52% of the patients showed drug levels below and 10% above the target range. In 35 out of 41 patients (85%) dose interventions led to adequate trough levels. Eventually, 64% of the total cohort reached adequate trough levels.
**Conclusions:** Dose optimization proved an effective tool to reach adequate trough levels in patients treated with imatinib, sunitinib and pazopanib. The percentage of patients with adequate trough levels increased from 38 to 64%. Therapeutic drug monitoring may add to the improvement of efficacy and reduction of toxicity and costs of these treatments.

Gepubliceerd: Br J Clin Pharmacol 2017 Oct;83(10):2195-204
Impact factor: 3.493

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**2. Decrease in Switches to 'Unsafe' Proton Pump Inhibitors After Communications About Interactions with Clopidogrel**
Kruik-Kolloffel WJ, van der Palen J, van Herk-Sukel MPP, Kruik HJ, Movig KLL

**Background:** In 2009 and 2010 medicines regulatory agencies published official safety statements regarding the concomitant use of proton pump inhibitors and clopidogrel. We wanted to investigate a change in prescription behaviour in prevalent gastroprotective drug users (2008-2011).
**Methods:** Data on drug use were retrieved from the Out-patient Pharmacy Database of the PHARMO Database Network. We used interrupted time series analyses (ITS) to estimate the impact of each safety statement on the number of gastroprotective drug switches around the start of clopidogrel and during clopidogrel use.
**Results:** After the first statement (June 2009), significantly fewer patients switched from another proton pump inhibitor to (es)omeprazole (-14.9%; 95% CI -22.6 to -7.3) at the moment they started clopidogrel compared to the period prior to this statement. After the adjusted statement in February 2010, the switch percentage to (es)omeprazole decreased further (-4.5%; 95% CI -8.1 to -0.9). We observed a temporary increase in switches from proton pump inhibitors to histamine 2-receptor antagonists after the first statement; the decrease in the reverse switch was statistically significant (-23.0%; 95% CI -43.1 to -2.9).
**Conclusions:** With ITS, we were able to demonstrate a decrease in switches from other proton pump inhibitors to (es)omeprazole and an increase of the reverse switch to almost 100%. We observed a partial and temporary switch to histamine 2-receptor antagonists. This effect of safety statements was shown for gastroprotective drug switches around the start of clopidogrel treatment.

Gepubliceerd: Clin Drug Investig 2017 Aug;37(8):787-94
Impact factor: 1.853

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**3. Nieuw model vereenvoudigt dosering protrombinecomplex**
Vrijkorte E, Movig K, Pleijhuis R, Oude Munnik T

Om op eenvoudige wijze de juiste dosering protrombinecomplex te kunnen bepalen, heeft het Medisch Spectrum Twente een model ontwikkeld in Evidencio. Via dit online platform voor het delen van predictie- en beslismodellen kunnen voorschrijvers nu snel en eenvoudig een *evidence-based* doseringsadvies vinden.

Gepubliceerd: Pharmaceutisch Weekblad 2017;152(38):22-3
Impact factor: 0

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Totale impact factor: 5.346
Gemiddelde impact factor: 1.782

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 5.346
Gemiddelde impact factor: 1.782

# Klinische fysica

**1. Micro-fabricated scaffolds lead to efficient remission of diabetes in mice**
Buitinga M, Assen F, Hanegraaf M, Wieringa P, Hilderink J, Moroni L, Truckenmuller R, van Blitterswijk C, Romer GW, Carlotti F, de Koning E, Karperien M, van Apeldoorn A

Despite the clinical success of intrahepatic islet transplantation in treating type 1 diabetes, factors specific to this transplantation site hinder long-term insulin independence. The adoption of alternative, extravascular sites likely improve islet survival and function, but few locations are able to sufficiently confine islets in order to facilitate engraftment. This work describes a porous microwell scaffold with a well-defined pore size and spacing designed to guarantee islet retention at an extrahepatic transplantation site and facilitate islet revascularization. Three techniques to introduce pores were characterized: particulate leaching; solvent casting on pillared wafers; and laser drilling. Our criteria of a maximum pore diameter of 40 mum were best achieved via laser drilling. Transplantation studies in the epididymal fat of diabetic mice elucidated the potential of this porous scaffold platform to restore blood glucose levels and facilitate islet engraftment. Six out of eight mice reverted to stable normoglycemia with a mean time to remission of 6.2 +/- 3.2 days, which was comparable to that of the gold standard of renal subcapsular islet grafts. In contrast, when islets were transplanted in the epididymal fat pad without a microwell scaffold, only two out of seven mice reverted to stable normoglycemia. Detailed histological evaluation four weeks after transplantation found a comparable vascular density in scaffold-seeded islets, renal subcapsular islets and native pancreatic islets. However, the vascularization pattern in scaffold-seeded islets was more inhomogeneous compared to native pancreatic islets with a higher vascular density in the outer shell of the islets compared to the inner core. We also observed a corresponding decrease in the beta-cell density in the islet core. Despite this, our data indicated that islets transplanted in the microwell scaffold platform were able to maintain a viable beta-cell population and restore glycemic control. Furthermore, we demonstrated that the microwell scaffold platform facilitated detailed analysis at a subcellular level to correlate design parameters with functional physiological observations.

Gepubliceerd: Biomaterials 2017 Aug;135:10-22
Impact factor: 8.402

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**2. Predicting success of vagus nerve stimulation (VNS) from EEG symmetry**
Hilderink J, Tjepkema-Cloostermans MC, Geertsema A, Glastra-Zwiers J, de Vos CC

**Purpose:** Vagus nerve stimulation (VNS) has shown to be an effective treatment for drug resistant epilepsy, with achieving more than 50% seizure reduction in one third of the treated patients. In order to predict which patients will profit from VNS, we previously found that a low pairwise derived Brain Symmetry Index (pdBSI) could potentially predict good responders to VNS treatment. These findings however have to be validated before they can be generalized.
**Methods:** 39 patients (age 18-68 years) with medically intractable epilepsy who were referred for an implanted VNS system were included. Routine EEG registrations, recorded before implantation, were analyzed. Artefact-free epochs with eyes open and eyes closed were quantitatively analyzed. The pdBSI was tested for relation with VNS outcome one year after surgery.
**Results:** Twenty-three patients (59%) obtained a reduction in seizure frequency, of whom ten (26%) had a reduction of at least 50% (good responders) and thirteen (33%) a reduction of less than 50% (moderate responders). Sixteen patients without seizure reduction are defined as non-responders. No significant differences were found in the pdBSI of good responders (mean 0.27), moderate responders (mean 0.26) and non-responders (mean 0.25) ($p>0.05$). Besides seizure reduction, many patients (56%) reported additional positive effects of VNS in terms of seizure duration, seizure intensity and/or postictal recovery.
**Conclusion:** EEG features that correlate with VNS therapy outcome may enable better patient selection and prevent unnecessary VNS surgery. Contrary to earlier findings, this validation study suggests that pdBSI might not be helpful to predict VNS therapy outcome.

Gepubliceerd: Seizure 2017 May;48:69-73
Impact factor: 2.448

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Totale impact factor: 10.850
Gemiddelde impact factor: 5.425

Aantal artikelen 1e, 2e of laatste auteur: 2.448
Totale impact factor: 1
Gemiddelde impact factor: 2.448

# Klinische psychologie

**1. Cognitive Behavioral Intervention Compared to Telephone Counseling Early after Mild Traumatic Brain Injury: A Randomized Trial**
Scheenen ME, Visser-Keizer AC, de Koning ME, van der Horn HJ, van de Sande P, van Kessel M, van der Naalt J, Spikman JM

Many patients do not return to work (RTW) after mild traumatic brain injury (mTBI) because of persistent complaints that are often resistant to therapy in the chronic phase. Recent studies suggest that psychological interventions should be implemented early post-injury to prevent patients from developing chronic complaints. This study is a randomized, controlled trial that examines the effectiveness of a newly developed cognitive behavioral therapy (CBT) intervention (CBTi) compared to telephonic counseling (TC) in at-risk mTBI patients (patients with high reports of early complaints). Patients underwent either five sessions of CBT treatment or five phone conversations starting 4-6 weeks post-trauma. The main outcome measure was RTW 6 and 12 months post-trauma. Secondary measures comprised functional outcome at 6 and 12 months, and depression, anxiety, and reported post-traumatic complaints at 3, 6, and 12 months post-injury. After excluding dropouts, CBTi consisted of 39 patients and TC of 45 patients. No significant differences were found with regard to RTW, with 65% of CBTi patients and 67% of TC patients reporting a RTW at previous level. However, TC patients reported fewer complaints at 3 (8 vs. 6; p = 0.010) and 12 months post-injury (9 vs. 5; p = 0.006), and more patients in the TC group showed a full recovery 12 months post-injury compared to the CBTi group (62% vs. 39%). The results of this study suggest that early follow-up of at-risk patients can have a positive influence on patients' well-being, and that a low-intensive, low-cost telephonic intervention might be more effective than a CBT intervention at improving outcome in at-risk patients.

Gepubliceerd: J Neurotrauma 2017 May 17;34(19):2713-20
Impact factor: 5.190

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Totale impact factor: 5.190
Gemiddelde impact factor: 5.190

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

# Longziekten

**1. The predictive value of an adjusted COPD assessment test score on the risk of respiratory-related hospitalizations in severe COPD patients**
Barton CA, Bassett KL, Buckman J, Effing TW, Frith PA, van der Palen J, Sloots JM

We evaluated whether a chronic obstructive pulmonary disease (COPD) assessment test (CAT) with adjusted weights for the CAT items could better predict future respiratory-related hospitalizations than the original CAT. Two focus groups (respiratory nurses and physicians) generated two adjusted CAT algorithms. Two multivariate logistic regression models for infrequent (</=1/year) versus frequent (>1/year) future respiratory-related hospitalizations were defined: one with the adjusted CAT score that correlated best with future hospitalizations and one with the original CAT score. Patient characteristics related to future hospitalizations ( p </= 0.2) were also entered. Eighty-two COPD patients were included. The CAT algorithm derived from the nurse focus group was a borderline significant predictor of hospitalization risk (odds ratio (OR): 1.07; 95% confidence interval (CI): 1.00-1.14; p = 0.050) in a model that also included hospitalization frequency in the previous year (OR: 3.98; 95% CI: 1.30-12.16; p = 0.016) and anticholinergic risk score (OR: 3.08; 95% CI: 0.87-10.89; p = 0.081). Presence of ischemic heart disease and/or heart failure appeared 'protective' (OR: 0.17; 95% CI: 0.05-0.62; p = 0.007). The original CAT score was not significantly associated with hospitalization risk. In conclusion, as a predictor of respiratory-related hospitalizations, an adjusted CAT score was marginally significant (although the original CAT score was not). 'Previous respiratory-related hospitalizations' was the strongest factor in this equation.

Gepubliceerd: Chron Respir Dis 2017 Feb;14(1):72-84
Impact factor: 1.818

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**2. Exhaled breath profiles in the monitoring of loss of control and clinical recovery in asthma**
Brinkman P, van de Pol MA, Gerritsen MG, Bos LD, Dekker T, Smids BS, Sinha A, Majoor CJ, Sneeboer MM, Knobel HH, Vink TJ, de Jongh FH, Lutter R, Sterk PJ, Fens N

**Background:** Asthma is a chronic inflammatory airway disease, associated with episodes of exacerbations. Therapy with inhaled corticosteroids (ICS) targets airway inflammation, which aims to maintain and restore asthma control. Clinical features are only modestly associated with airways inflammation. Therefore, we hypothesized that

exhaled volatile metabolites identify longitudinal changes between clinically stable episodes and loss of asthma control. **Objectives:** To determine whether exhaled volatile organic compounds (VOCs) as measured by gas-chromatography/mass-spectrometry (GC/MS) and electronic nose (eNose) technology discriminate between clinically stable and unstable episodes of asthma.
**Methods:** Twenty-three patients with (partly) controlled mild to moderate persistent asthma using ICS were included in this prospective steroid withdrawal study. Exhaled metabolites were measured at baseline, during loss of control and after recovery. Standardized sampling of exhaled air was performed, after which samples were analysed by GC/MS and eNose. Univariate analysis of covariance (ANCOVA), followed by multivariate principal component analysis (PCA) was used to reduce data dimensionality. Next paired t tests were utilized to analyse within-subject breath profile differences at the different time-points. Finally, associations between exhaled metabolites and sputum inflammation markers were examined.
**Results:** Breath profiles by eNose showed 95% (21/22) correct classification for baseline vs loss of control and 86% (19/22) for loss of control vs recovery. Breath profiles using GC/MS showed accuracies of 68% (14/22) and 77% (17/22) for baseline vs loss of control and loss of control vs recovery, respectively. Significant associations between exhaled metabolites captured by GC/MS and sputum eosinophils were found (Pearson r>/=.46, P<.01).
**Conclusions & clinical relevance:** Loss of asthma control can be discriminated from clinically stable episodes by longitudinal monitoring of exhaled metabolites measured by GC/MS and particularly eNose. Part of the uncovered biomarkers was associated with sputum eosinophils. These findings provide proof of principle for monitoring and identification of loss of asthma control by breathomics.

Gepubliceerd: Clin Exp Allergy 2017 Jun 19;47(9):1159-69
Impact factor: 5.264

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**3. Comparing the 2007 and 2011 GOLD Classifications as Predictors of all-Cause Mortality and Morbidity in COPD**
Brusse-Keizer M, Klatte M, Zuur-Telgen M, Koehorst-Ter Huurne K, van der Palen J, VanderValk P

To better classify patients with chronic obstructive pulmonary disease (COPD) for prognostic purposes and to tailor treatment, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 classification was revised in 2011. The primary aim of the current data analyses was to evaluate the accuracy of the GOLD 2007 and 2011 GOLD classifications to predict all-cause mortality and morbidity in a well-described COPD cohort. The prognostic values of both GOLD classifications,

expressed as the C-statistic, were assessed in the Cohort of Mortality and Inflammation in COPD (COMIC) study of 795 COPD patients, with a follow-up of 3 years. Outcomes were all-cause mortality and morbidity. Morbidity was defined as time until first COPD-related hospitalisation and time until first community-acquired pneumonia (CAP). The prognostic value of the GOLD 2011 classification was compared between symptom classification based on the modified Medical Research Council (mMRC) score and the Clinical COPD Questionnaire (CCQ) scores with two different thresholds. Although the GOLD 2011 CCQ classification had the highest accuracy to predict mortality and morbidity in our study, the C-statistics differed only numerically. Furthermore, our study showed that the instrument used to determine the level of symptoms in the GOLD 2011 classification has not only important consequences on the mortality prognosis, but also affects the morbidity prognosis in COPD. Therefore, patients' estimated prognosis could alter when different types of tools are used to evaluate the prognosis.

Gepubliceerd: COPD 2017 Feb;14(1):7-14
Impact factor: 2.576

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**4. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests**
Coates AL, Wanger J, Cockcroft DW, Culver BH, Diamant Z, Gauvreau G, Hall GL, Hallstrand TS, Horvath I, de Jongh FHC, Joos G, Kaminsky DA, Laube BL, Leuppi JD, Sterk PJ

This international task force report updates general considerations for bronchial challenge testing and the performance of the methacholine challenge test. There are notable changes from prior recommendations in order to accommodate newer delivery devices. Rather than basing the test result upon a methacholine concentration (provocative concentration (PC20) causing a 20% fall in forced expiratory volume in 1 s (FEV1)), the new recommendations base the result upon the delivered dose of methacholine causing a 20% fall in FEV1 (provocative dose (PD20)). This end-point allows comparable results from different devices or protocols, thus any suitable nebuliser or dosimeter may be used, so long as the delivery characteristics are known. Inhalation may be by tidal breathing using a breath-actuated or continuous nebuliser for 1 min (or more), or by a dosimeter with a suitable breath count. Tests requiring maximal inhalations to total lung capacity are not recommended because the bronchoprotective effect of a deep breath reduces the sensitivity of the test.

Gepubliceerd: Eur Respir J 2017 May;49(5)

Impact factor: 10.569

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**5. Analysing Tuberculosis Cases Among Healthcare Workers to Inform Infection Control Policy and Practices**
de Vries G, van Hunen R, Meerstadt-Rombach FS, van der Valk PDLP, Vermue M, Keizer ST

**Objective:** To determine the number and proportion of healthcare worker (HCW) tuberculosis (TB) cases infected while working in healthcare institutions in the Netherlands and to learn from circumstances that led to these infections. DESIGN Cohort analysis.
**Methods:** We included all HCW TB patients reported to the Netherlands TB Register from 2000 to 2015. Using data from this register, including DNA fingerprints of the bacteria profile and additional information from public health clinics, HCW TB cases were classified into 4 categories: (1) infected during work in the Netherlands, (2) infected in the community, (3) infected outside the Netherlands, or (4) outside these 3 categories. An in-depth analysis of category 1 cases was performed to identify factors contributing to patient-to-HCW transmission.
**Results:** In total, 131 HCW TB cases were identified: 32 cases (24%) in category 1; 13 cases (10%) in category 2; 42 cases (32%) in category 3; and 44 cases (34%) in category 4. The annual number of HCW TB cases (P<.05), the proportion among reported cases (P<.01), and the number of category 1 HCW TB cases (P=.12) all declined over the study period. Delayed diagnosis in a TB patient was the predominant underlying factor of nosocomial transmission in 47% of category 1 HCW TB patients, most of whom were subsequently identified in a contact investigation. Performing high-risk procedures was the main contributing factor in the other 53% of cases.
**Conclusion:** In low-incidence countries, every HCW TB case should warrant timely and thorough investigation to help further define and fine-tune the HCW screening policy and to monitor its proper implementation. Infect Control Hosp Epidemiol 2017;38:976-982.

Gepubliceerd: Infect Control Hosp Epidemiol 2017 Aug;38(8):976-82
Impact factor: 3.550

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**6. Breath detection by transcutaneous electromyography of the diaphragm and the Graseby capsule in preterm infants**
de Waal CG, Kraaijenga JV, Hutten GJ, de Jongh FH, van Kaam AH

**Objective:** To compare triggering, breath detection and delay time of the Graseby capsule (GC) and transcutaneous electromyography of the diaphragm (dEMG) in spontaneous breathing preterm infants.
**Methods:** In this observational study, a 30 minutes respiration measurement was conducted by respiratory inductance plethysmography (RIP), the GC, and dEMG in stable preterm infants. Triggering was investigated with an in vitro set-up using the Infant Flow((R)) SiPAP(TM) system. The possibility to optimize breath detection was tested by developing new algorithms with the abdominal RIP band (RIPAB ) as gold standard. In a subset of breaths, the delay time was calculated between the inspiratory onset in the RIPAB signal and in the GC and dEMG signal.
**Results:** Fifteen preterm infants with a mean gestational age of 28 +/- 2 weeks and a mean birth weight of 1086 +/- 317 g were included. In total, 14 773 breaths were analyzed. Based on the GC and dEMG signal, the Infant Flow((R)) SiPAP system, respectively, triggered 67.8% and 62.6% of the breaths. Breath detection was improved to 99.9% for the GC and 113.4% for dEMG in new algorithms. In 1492 stable breaths, the median delay time of inspiratory onset detection was +154 ms (IQR +118 to +164) in the GC and -50 ms (IQR -90 to -22) in the dEMG signal.
**Conclusion:** Breath detection using the GC can be improved by optimizing the algorithm. Transcutaneous dEMG provides similar breath detection but with the advantage of detecting the onset of inspiration earlier than the GC.

Gepubliceerd: Pediatr Pulmonol 2017 Dec;52(12):1578-82
Impact factor: 2.758

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**7. Electrical activity of the diaphragm during nCPAP and high flow nasal cannula**
de Waal CG, Hutten GJ, Kraaijenga JV, de Jongh FH, van Kaam AH

**Objective:** To determine if the electrical activity of the diaphragm, as measure of neural respiratory drive and breathing effort, changes over time in preterm infants transitioned from nasal continuous positive airway pressure (nCPAP) to high flow nasal cannula (HFNC). DESIGN: Prospective observational study.
**Setting:** Neonatal intensive care unit.
**Patients:** Stable preterm infants transitioned from nCPAP to HFNC using a 1:1 pressure to flow ratio.
**Interventions:** The electrical activity of the diaphragm was measured by transcutaneous electromyography (dEMG) from 30 min before until 3 hours after the transition.
**Main outcome measures:** At eight time points after the transition to HFNC, diaphragmatic activity was compared with the baseline on nCPAP. Percentage

change in amplitudedEMG, peakdEMG and tonicdEMG were calculated. Furthermore, changes in respiratory rate, heart rate and fraction of inspired oxygen (FiO2) were analysed.
**Results:** Thirty-two preterm infants (mean gestational age: 28.1+/-2.2 weeks, mean birth weight: 1118+/-368 g) were included. Compared with nCPAP, the electrical activity of the diaphragm did not change during the first 3 hours on HFNC (median (IQR) change in amplitudedEMG at t=180 min: 2.81% (-21.51-14.10)). The respiratory rate, heart rate and FiO2 remained stable during the 3-hour measurement.
**Conclusions:** Neural respiratory drive and breathing effort assessed by electrical activity of the diaphragm is similar in the first 3 hours after transitioning stable preterm infants from nCPAP to HFNC with a 1:1 pressure-to-flow ratio.

Gepubliceerd: Arch Dis Child Fetal Neonatal Ed 2017 Sep;102(5):F434-F438
Impact factor: 4.099

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**8. The TL,NO /TL,CO ratio cannot be used to exclude pulmonary embolism**
Fabius TM, Eijsvogel MM, van der Lee I, Brusse-Keizer M, de Jongh FH

**Background:** The existing screening modalities for pulmonary embolism (PE), such as D-dimer and clinical prediction rules, have low positive predictive values. With its capability to indicate pulmonary vascular abnormalities, the ratio of the transfer factor of the lungs for nitric oxide and the transfer factor of the lungs for carbon monoxide (TL,NO /TL,CO ) might be an additional discriminating parameter.
**Methods:** Carbon monoxide/Nitric oxide diffusion measurements were performed on unselected patients seen on the emergency department for which due to suspected PE a computed tomography pulmonary angiogram (CTPA) was ordered.
**Results:** A total of 28 patients were included, PE was found in 12 on CTPA. Median TL,NO /TL,CO ratio was 4.09 (interquartile range (IQR) 3.83-4.40) in the no PE group versus 4.00 (IQR 3.78-4.32) in the PE group (P = 0.959). Median alveolar volume was 77.1% of predicted in the no PE group versus 71.0% of predicted in the PE group (P = 0.353). Median TL,CO was 75.8% of predicted in the no PE group versus 68.8% of predicted in the PE group (P = 0.120). Median TL,NO was 69.3% of predicted in the no PE group versus 60.5% of predicted in the PE group (P = 0.078).
**Conclusion:** The presented data indicate that the TL,NO /TL,CO ratio cannot be used to exclude PE.

Gepubliceerd: Clin Physiol Funct Imaging 2017 Jul;37(4):400-4
Impact factor: 2.300

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**9. Influence of lung nodule margin on volume- and diameter-based reader variability in CT lung cancer screening**
Han D, Heuvelmans MA, Vliegenthart R, Rook M, Dorrius MD, de Jonge GJ, Walter JE, van Ooijen PMA, de Koning HJ, Oudkerk M

**Objective:** To evaluate the influence of nodule margin on inter- and intrareader variability in manual diameter measurements and semi-automatic volume measurements of solid nodules detected in low-dose CT lung cancer screening.
**Methods:** 25 nodules of each morphological category (smooth, lobulated, spiculated and irregular) were randomly selected from 93 participants of the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON). Semi-automatic volume measurements were performed using Syngo LungCARE(R) software (Version Somaris/5 VB10A-W, Siemens, Forchheim, Germany). Three radiologists independently measured mean diameters manually. Impact of nodule margin on interreader variability was evaluated based on systematic error and 95% limits of agreement. Interreader variability was compared with the nodule growth cut-off as used in Lung CT Screening Reporting and Data System (LungRADS; +1.5-mm diameter) and the Dutch-Belgian Randomized Lung Cancer Screening Trial(acronym: NELSON) /British Thoracic Society (+25% volume).
**Results:** For manual diameter measurements, a significant systematic error (up to 1.2 mm) between readers was found in all morphological categories. For semi-automatic volume measurements, no statistically significant systematic error was found. The interreader variability in mean diameter measurements exceeded the 1.5-mm cut-off for nodule growth for all morphological categories [smooth: +/-1.9 mm (+27%), lobulated: +/-2.0 mm (+33%), spiculated: +/-3.5 mm (+133%), irregular: +/-4.5 mm (+200%)]. The 25% vol growth cut-off was exceeded slightly for spiculated [28% (+12%)] and irregular [27% (+8%)] nodules.
**Conclusion:** Lung nodule sizing based on manual diameter measurement is affected by nodule margin. Interreader variability increases especially for nodules with spiculated and irregular margins, and causes substantial misclassification of nodule growth. This effect is almost neglectable for semi-automated volume measurements. Semi-automatic volume measurements are superior for both size and growth determination of pulmonary nodules. Advances in knowledge: Nodule assessment based on manual diameter measurements is susceptible to nodule margin. This effect is almost neglectable for semi-automated volume measurements. The larger interreader variability for manual diameter measurement results in inaccurate lung nodule growth detection and size classification.

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Impact factor: 2.050

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**10. Volume versus diameter assessment of small pulmonary nodules in CT lung cancer screening**
Han D, Heuvelmans MA, Oudkerk M

Currently, lung cancer screening by low-dose chest CT is implemented in the United States for high-risk persons. A disadvantage of lung cancer screening is the large number of small-to-intermediate sized lung nodules, detected in around 50% of all participants, the large majority being benign. Accurate estimation of nodule size and growth is essential in the classification of lung nodules. Currently, manual diameter measurements are the standard for lung cancer screening programs and routine clinical care. However, European screening studies using semi-automated volume measurements have shown higher accuracy and reproducibility compared to diameter measurements. In addition to this, with the optimization of CT scan techniques and reconstruction parameters, as well as advances in segmentation software, the accuracy of nodule volume measurement can be improved even further. The positive results of previous studies on volume and diameter measurements of lung nodules suggest that manual measurements of nodule diameter may be replaced by semi-automated volume measurements in the (near) future.

Gepubliceerd: Transl Lung Cancer Res 2017 Feb;6(1):52-61
Impact factor: 0

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**11. Early lung cancer detection by low-dose CT screening: therapeutic implications**
Heuvelmans MA, Groen HJ, Oudkerk M

**Introduction:** Lung cancer screening by low-dose chest computed tomography is currently implemented in the U.S. After implementation of screening, a stage shift may be observed from around 15% stage I non-small cell lung cancers (NSCLCs) in routine clinical practice to up to 70% in screening patients. This indicates a move in treatment options from advanced to early lung cancers, especially in those with small suspected intrapulmonary nodules. Areas covered: We have reviewed the current status of lung cancer screening from the different randomized controlled lung cancer screening studies and the clinical evidence so far for both surgical and non-surgical treatment options for (screen-detected) stage I NSCLC. Furthermore, we provide a step-wise approach for the treatment of stage I NSCLC. Expert Commentary: Recommended treatment for stage I NSCLC remains (VATS) lobectomy in case of a medically operable patient, VATS sublobar resection for subcentimeter nodules, and SBRT otherwise. Currently, there is too limited evidence for the value of ablative

techniques in curative treatment of early stage NSCLC. Therefore, these therapies should only be used in expert centers for selected patients in clinical studies.

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Impact factor: 2.432

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**12. Management of baseline and new sub-solid nodules in CT lung cancer screening**
Heuvelmans MA, Walter JE, Oudkerk M

Gepubliceerd: Expert Rev Respir Med 2017 Nov 1;1-3
Impact factor: 2.432

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**13. Quantification of growth patterns of screen-detected lung cancers: The NELSON study**
Heuvelmans MA, Vliegenthart R, de Koning HJ, Groen HJM, van Putten MJAM, Yousaf-Khan U, Weenink C, Nackaerts K, de Jong PA, Oudkerk M

**Objectives:** Although exponential growth is assumed for lung cancer, this has never been quantified in vivo. Aim of this study was to evaluate and quantify growth patterns of lung cancers detected in the Dutch-Belgian low-dose computed tomography (CT) lung cancer screening trial (NELSON), in order to elucidate the development and progression of early lung cancer. MATERIALS AND
**Methods:** Solid lung nodules found at >/=3 CT examinations before lung cancer diagnosis were included. Lung cancer volume (V) growth curves were fitted with a single exponential, expressed as V=V1 exp(t/tau), with t time from baseline (days), V1 estimated baseline volume (mm3), and tau estimated time constant. The R2 coefficient of determination was used to evaluate goodness of fit. Overall volume-doubling time for the individual lung cancer is given by tau*log(2).
**Results:** Forty-seven lung cancers in 46 participants were included. Forty participants were male (87.0%); mean age was 61.7 years (standard deviation, 6.2 years). Median nodule size at baseline was 99.5mm3 (IQR: 46.8-261.8mm3). Nodules were followed for a median of 770 days (inter-quartile range: 383-1102 days) before lung cancer diagnosis. One cancer (2.1%) was diagnosed after six CT examinations, six cancers (12.8%) were diagnosed after five CTs, 14 (29.8%) after four CTs, and 26 cancers (55.3%) after three CTs. Lung cancer growth could be described by an exponential function with excellent goodness of fit (R2 0.98). Median overall volume-doubling time was 348 days (inter-quartile range: 222-492 days).

**Conclusion:** This study based on CT lung cancer screening provides in vivo evidence that growth of cancerous small-to-intermediate sized lung nodules detected at low-dose CT lung cancer screening can be described by an exponential function such as volume-doubling time.

Gepubliceerd: Lung Cancer 2017 Jun;108:48-54
Impact factor: 4.294

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**14. Relationship between nodule count and lung cancer probability in baseline CT lung cancer screening: The NELSON study**
Heuvelmans MA, Walter JE, Peters RB, Bock GH, Yousaf-Khan U, Aalst CMV, Groen HJM, Nackaerts K, Ooijen PMV, Koning HJ, Oudkerk M, Vliegenthart R

**Objectives:** To explore the relationship between nodule count and lung cancer probability in baseline low-dose CT lung cancer screening. MATERIALS AND **Methods:** Included were participants from the NELSON trial with at least one baseline nodule (3392 participants [45% of screen-group], 7258 nodules). We determined nodule count per participant. Malignancy was confirmed by histology. Nodules not diagnosed as screen-detected or interval cancer until the end of the fourth screening round were regarded as benign. We compared lung cancer probability per nodule count category.
**Results:** 1746 (51.5%) participants had one nodule, 800 (23.6%) had two nodules, 354 (10.4%) had three nodules, 191 (5.6%) had four nodules, and 301 (8.9%) had>4 nodules. Lung cancer in a baseline nodule was diagnosed in 134 participants (139 cancers; 4.0%). Median nodule count in participants with only benign nodules was 1 (Inter-quartile range [IQR]: 1-2), and 2 (IQR 1-3) in participants with lung cancer (p=NS). At baseline, malignancy was detected mostly in the largest nodule (64/66 cancers). Lung cancer probability was 62/1746 (3.6%) in case a participant had one nodule, 33/800 (4.1%) for two nodules, 17/354 (4.8%) for three nodules, 12/191 (6.3%) for four nodules and 10/301 (3.3%) for>4 nodules (p=NS).
**Conclusion:** In baseline lung cancer CT screening, half of participants with lung nodules have more than one nodule. Lung cancer probability does not significantly change with the number of nodules. Baseline nodule count will not help to differentiate between benign and malignant nodules. Each nodule found in lung cancer screening should be assessed separately independent of the presence of other nodules.

Gepubliceerd: Lung Cancer 2017 Nov;113:45-50
Impact factor: 4.294

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**15. Data analysis of electronic nose technology in lung cancer: generating prediction models by means of Aethena**
Kort S, Brusse-Keizer M, Gerritsen JW, van der Palen J

**Introduction:** Only 15% of lung cancer cases present with potentially curable disease. Therefore, there is much interest in a fast, non-invasive tool to detect lung cancer earlier. Exhaled breath analysis using electronic nose technology measures volatile organic compounds (VOCs) in exhaled breath that are associated with lung cancer.
**Methods:** The diagnostic accuracy of the Aeonose is currently being studied in a multi-centre, prospective study in 210 subjects suspected for lung cancer, where approximately half will have a confirmed diagnosis and the other half will have a rejected diagnosis of lung cancer. We will also include 100-150 healthy control subjects. The eNose Company (provider of the Aeonose) uses a software program, called Aethena, comprising pre-processing, data compression and neural networks to handle big data analyses. Each individual exhaled breath measurement comprises a data matrix with thousands of conductivity values. This is followed by data compression using a Tucker3-like algorithm, resulting in a vector. Subsequently, model selection takes place after entering vectors with different presets in an artificial neural network to train and evaluate the results. Next, a 'judge model' is formed, which is a combination of models for optimizing performance. Finally, two types of cross-validation, being 'leave-10%-out' cross-validation and 'bagging', are used when recalculating the judge models. These judge models are subsequently used to classify new, blind measurements.
**Discussion:** Data analysis in eNose technology is principally based on generating prediction models that need to be validated internally and externally for eventual use in clinical practice. This paper describes the analysis of big data, captured by eNose technology in lung cancer. This is done by means of generating prediction models with Aethena, a data analysis program specifically developed for analysing VOC data.

Gepubliceerd: J Breath Res 2017 Jun 1;11(2):026006
Impact factor: 4.318

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**16. Classifying Apnea of Prematurity by Transcutaneous Electromyography of the Diaphragm**
Kraaijenga JV, Hutten GJ, de Waal CG, de Jongh FH, Onland W, van Kaam AH

**Background:** Treatment of apnea is highly dependent on the type of apnea. Chest impedance (CI) has inaccuracies in monitoring respiration, which compromises

accurate apnea classification. Electrical activity of the diaphragm measured by transcutaneous electromyography (EMG) is feasible in preterm infants and might improve the accuracy of apnea classification. **Objectives:** To compare the accuracy of apnea classification based on diaphragmatic EMG (dEMG) and CI tracings in preterm infants.
**Methods:** Fifteen cases of central apnea, 5 of obstructive apnea, and 10 of mixed apnea were selected from recordings containing synchronized continuous tracings of respiratory inductive plethysmography (RIP), airway flow, heart rate (HR), oxygen saturation (SpO2), and breathing activity measured by dEMG and CI. Twenty-two assessors (neonatologists, pediatricians-in-training, and nurses) classified each apnea twice; once based on dEMG, HR, and SpO2 tracings, and once based on CI, HR, and SpO2. The assessors were blinded to the type of respiratory tracing (dEMG or CI) and to the RIP and flow tracings.
**Results:** In total 1,320 assessments were performed, and in 71.1% the apnea was classified correctly. Subgroup analysis based on respiratory tracing showed that 74.8% of the dEMG tracings were classified correctly compared to 67.3% of the CI tracings ($p < 0.001$). This improved apnea classification based on dEMG was present for central (86.7 vs. 80.3%, $p < 0.02$) and obstructive (56.4 vs. 32.7%, $p < 0.001$) apnea. The improved apnea classification based on dEMG tracing was independent of the type of assessor.
**Conclusion:** Transcutaneous dEMG improves the accuracy of apnea classification when compared to CI in preterm infants, making this technique a promising candidate for future monitoring systems.

Gepubliceerd: Neonatology 2017 Dec 1;113(2):140-5
Impact factor: 2.598

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**17. Diaphragmatic activity during weaning from respiratory support in preterm infants**
Kraaijenga JV, de Waal CG, Hutten GJ, de Jongh FH, van Kaam AH

**Objective:** To determine if weaning from nasal continuous positive airway pressure (nCPAP) to lesser supportive low flow nasal cannula (LFNC) results in a change in electrical activity of the diaphragm in preterm infants.
**Design:** Prospective observational study.
**Setting:** Neonatal intensive care unit. PATIENTS: Stable preterm infants weaned from nCPAP to LFNC (1 L/min).
**Main outcome measures:** Change in diaphragmatic activity, expressed as amplitude, peak and tonic activity, measured by transcutaneous electromyography

(dEMG) from 30 min before (baseline) until 180 min after weaning. Subgroup analysis was performed based on success or failure of the weaning attempt.
**Results:** Fifty-nine preterm infants (gestational age: 29.0+/-2.4 weeks, birth weight: 1210+/-443 g) accounting for 74 weaning attempts were included. A significant increase in dEMG amplitude (median, IQR: 21.3%, 3.6-41.4), peak (22.1%, 8.7-40.5) and tonic activity (14.3%, -1.9-38.1) was seen directly after weaning. This effect slowly decreased over time. Infants failing the weaning attempt tended to have a higher diaphragmatic activity than those successfully weaned.
**Conclusions:** Weaning from nCPAP to LFNC leads to an increase in diaphragmatic activity measured by dEMG and is most prominent in preterm infants failing the weaning attempt. dEMG monitoring might be a useful parameter to guide weaning from respiratory support in preterm infants.

Gepubliceerd: Arch Dis Child Fetal Neonatal Ed 2017 Jul;102(4):F307-F311
Impact factor: 4.099

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**18. Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease**
Lenferink A, Brusse-Keizer M, van der Valk PD, Frith PA, Zwerink M, Monninkhof EM, van der Palen J, Effing TW

**Background:** Chronic Obstructive Pulmonary Disease (COPD) self-management interventions should be structured but personalised and often multi-component, with goals of motivating, engaging and supporting the patients to positively adapt their behaviour(s) and develop skills to better manage disease. Exacerbation action plans are considered to be a key component of COPD self-management interventions. Studies assessing these interventions show contradictory results. In this Cochrane Review, we compared the effectiveness of COPD self-management interventions that include action plans for acute exacerbations of COPD (AECOPD) with usual care.
**Objectives:** To evaluate the efficacy of COPD-specific self-management interventions that include an action plan for exacerbations of COPD compared with usual care in terms of health-related quality of life, respiratory-related hospital admissions and other health outcomes. SEARCH
**Methods:** We searched the Cochrane Airways Group Specialised Register of trials, trials registries, and the reference lists of included studies to May 2016.
**Selection criteria:** We included randomised controlled trials evaluating a self-management intervention for people with COPD published since 1995. To be eligible for inclusion, the self-management intervention included a written action plan for AECOPD and an iterative process between participant and healthcare provider(s) in which feedback was provided. We excluded disease management programmes

classified as pulmonary rehabilitation or exercise classes offered in a hospital, at a rehabilitation centre, or in a community-based setting to avoid overlap with pulmonary rehabilitation as much as possible.
**Data collection and analysis:** Two review authors independently assessed trial quality and extracted data. We resolved disagreements by reaching consensus or by involving a third review author. Study authors were contacted to obtain additional information and missing outcome data where possible. When appropriate, study results were pooled using a random-effects modelling meta-analysis. The primary outcomes of the review were health-related quality of life (HRQoL) and number of respiratory-related hospital admissions.
**Main results:** We included 22 studies that involved 3,854 participants with COPD. The studies compared the effectiveness of COPD self-management interventions that included an action plan for AECOPD with usual care. The follow-up time ranged from two to 24 months and the content of the interventions was diverse.Over 12 months, there was a statistically significant beneficial effect of self-management interventions with action plans on HRQoL, as measured by the St. George's Respiratory Questionnaire (SGRQ) total score, where a lower score represents better HRQoL. We found a mean difference from usual care of -2.69 points (95% CI -4.49 to -0.90; 1,582 participants; 10 studies; high-quality evidence). Intervention participants were at a statistically significant lower risk for at least one respiratory-related hospital admission compared with participants who received usual care (OR 0.69, 95% CI 0.51 to 0.94; 3,157 participants; 14 studies; moderate-quality evidence). The number needed to treat to prevent one respiratory-related hospital admission over one year was 12 (95% CI 7 to 69) for participants with high baseline risk and 17 (95% CI 11 to 93) for participants with low baseline risk (based on the seven studies with the highest and lowest baseline risk respectively).There was no statistically significant difference in the probability of at least one all-cause hospital admission in the self-management intervention group compared to the usual care group (OR 0.74, 95% CI 0.54 to 1.03; 2467 participants; 14 studies; moderate-quality evidence). Furthermore, we observed no statistically significant difference in the number of all-cause hospitalisation days, emergency department visits, General Practitioner visits, and dyspnoea scores as measured by the (modified) Medical Research Council questionnaire for self-management intervention participants compared to usual care participants. There was no statistically significant effect observed from self-management on the number of COPD exacerbations and no difference in all-cause mortality observed (RD 0.0019, 95% CI -0.0225 to 0.0263; 3296 participants; 16 studies; moderate-quality evidence). Exploratory analysis showed a very small, but significantly higher respiratory-related mortality rate in the self-management intervention group compared to the usual care group (RD 0.028, 95% CI 0.0049 to 0.0511; 1219 participants; 7 studies; very low-quality evidence).Subgroup analyses showed significant improvements in HRQoL in self-management interventions with a smoking cessation programme (MD -4.98, 95%

CI -7.17 to -2.78) compared to studies without a smoking cessation programme (MD -1.33, 95% CI -2.94 to 0.27, test for subgroup differences: Chi(2) = 6.89, df = 1, P = 0.009, I(2) = 85.5%). The number of behavioural change techniques clusters integrated in the self-management intervention, the duration of the intervention and adaptation of maintenance medication as part of the action plan did not affect HRQoL. Subgroup analyses did not detect any potential variables to explain differences in respiratory-related hospital admissions among studies.
**Authors' conclusions:** Self-management interventions that include a COPD exacerbation action plan are associated with improvements in HRQoL, as measured with the SGRQ, and lower probability of respiratory-related hospital admissions. No excess all-cause mortality risk was observed, but exploratory analysis showed a small, but significantly higher respiratory-related mortality rate for self-management compared to usual care.For future studies, we would like to urge only using action plans together with self-management interventions that meet the requirements of the most recent COPD self-management intervention definition. To increase transparency, future study authors should provide more detailed information regarding interventions provided. This would help inform further subgroup analyses and increase the ability to provide stronger recommendations regarding effective self-management interventions that include action plans for AECOPD. For safety reasons, COPD self-management action plans should take into account comorbidities when used in the wider population of people with COPD who have comorbidities. Although we were unable to evaluate this strategy in this review, it can be expected to further increase the safety of self-management interventions. We also advise to involve Data and Safety Monitoring Boards for future COPD self-management studies.

Gepubliceerd: Cochrane Database Syst Rev 2017 Aug 4;8:CD011682
Impact factor: 6.264

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**19. European position statement on lung cancer screening**
Oudkerk M, Devaraj A, Vliegenthart R, Henzler T, Prosch H, Heussel CP, Bastarrika G, Sverzellati N, Mascalchi M, Delorme S, Baldwin DR, Callister ME, Becker N, Heuvelmans MA, Rzyman W, Infante MV, Pastorino U, Pedersen JH, Paci E, Duffy SW, de Koning H, Field JK

Lung cancer screening with low-dose CT can save lives. This European Union (EU) position statement presents the available evidence and the major issues that need to be addressed to ensure the successful implementation of low-dose CT lung cancer screening in Europe. This statement identified specific actions required by the European lung cancer screening community to adopt before the implementation of low-dose CT lung cancer screening. This position statement recommends the

following actions: a risk stratification approach should be used for future lung cancer low-dose CT programmes; that individuals who enter screening programmes should be provided with information on the benefits and harms of screening, and smoking cessation should be offered to all current smokers; that management of detected solid nodules should use semi-automatically measured volume and volume-doubling time; that national quality assurance boards should be set up to oversee technical standards; that a lung nodule management pathway should be established and incorporated into clinical practice with a tailored screening approach; that non-calcified baseline lung nodules greater than 300 mm(3), and new lung nodules greater than 200 mm(3), should be managed in multidisciplinary teams according to this EU position statement recommendations to ensure that patients receive the most appropriate treatment; and planning for implementation of low-dose CT screening should start throughout Europe as soon as possible. European countries need to set a timeline for implementing lung cancer screening.

Gepubliceerd: Lancet Oncol 2017 Dec;18(12):e754-e766
Impact factor: 33.900

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**20. Blood eosinophilia as a marker of early and late treatment failure in severe acute exacerbations of COPD**

Prins HJ, Duijkers R, Lutter R, Daniels JM, van der Valk PD, Schoorl M, Kerstjens HA, van der Werf TS, Boersma WG

**Background:** Blood eosinophilia is frequently encountered in patients with AECOPD. However the impact of blood eosinophilia at admission in patients with AECOPD on outcome on the short and long term has not been extensively studied which was the objective of the present study.
**Methods:** We used data of 207 exacerbations from a randomized clinical trial on antibiotic prescription based upon CRP-levels versus GOLD guided strategy and analyzed the impact of blood eosinophils (>/=2% of total white cell count and eosinophil count >/=300 cell/microliter) on clinical outcome.
**Results:** 207 patients were included of whom 39 (18.8%) had eosinophilia >/=2%, 23 patients (11.1%) had blood eosinophil >/=300 cell/microliter. Eosinophilia was associated with shorter median length of stay in the eosinophilic groups(>/=2% and >/=300 cell/microliter) compared to the non-eosinophilic groups. Early treatment failure was reduced in the both the eosinophilic groups (>/=2% and >/=300 cell/microliter). Late treatment failure (day 11-30) did not differ between the groups. Relapse, was more frequent the eosinophilic groups (>/=2% and >/=300 cell/microliter), however in the latter group this did not reach statistical significance. Eosinophilia >/=2% was a risk factor for having relapse (eosinophilia >/=2%: HR =

2.351; 95%CI 1.335-4.139), whereas eosinophilia <2% was associated with a lower risk factor for having early treatment failure (HR = 0.339 95%CI 0.122-0.943).
**Conclusion:** We showed that blood eosinophilia at admission in patients with an AECOPD is associated with higher short-term treatment success rate. However, blood eosinophilia >/=2% predicts a less favorable outcome due to an increased risk of relapse.
**Clinical trial registration:** NCT01232140.

Gepubliceerd: Respir Med 2017 Oct;131:118-24
Impact factor: 3.217

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**21. A randomised open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices**
van der Palen J, Thomas M, Chrystyn H, Sharma RK, van der Valk PD, Goosens M, Wilkinson T, Stonham C, Chauhan AJ, Imber V, Zhu CQ, Svedsater H, Barnes NC

Errors in the use of different inhalers were investigated in patients naive to the devices under investigation in a multicentre, single-visit, randomised, open-label, cross-over study. Patients with chronic obstructive pulmonary disease (COPD) or asthma were assigned to ELLIPTA vs DISKUS (Accuhaler), metered-dose inhaler (MDI) or Turbuhaler. Patients with COPD were also assigned to ELLIPTA vs Handihaler or Breezhaler. Patients demonstrated inhaler use after reading the patient information leaflet (PIL). A trained investigator assessed critical errors (i.e., those likely to result in the inhalation of significantly reduced, minimal or no medication). If the patient made errors, the investigator demonstrated the correct use of the inhaler, and the patient demonstrated inhaler use again. Fewer COPD patients made critical errors with ELLIPTA after reading the PIL vs: DISKUS, 9/171 (5%) vs 75/171 (44%); MDI, 10/80 (13%) vs 48/80 (60%); Turbuhaler, 8/100 (8%) vs 44/100 (44%); Handihaler, 17/118 (14%) vs 57/118 (48%); Breezhaler, 13/98 (13%) vs 45/98 (46%; all Po0.001). Most patients (57-70%) made no errors using ELLIPTA and did not require investigator instruction. Instruction was required for DISKUS (65%), MDI (85%), Turbuhaler (71%), Handihaler (62%) and Breezhaler (56%). Fewer asthma patients made critical errors with ELLIPTA after reading the PIL vs: DISKUS (3/70 (4%) vs 9/70 (13%), P = 0.221); MDI (2/32 (6%) vs 8/32 (25%), P = 0.074) and significantly fewer vs Turbuhaler (3/60 (5%) vs 20/60 (33%), Po0.001). More asthma and COPD patients preferred ELLIPTA over the other devices (all P ?0.002). Significantly, fewer COPD patients using ELLIPTA made critical errors after reading the PIL vs other inhalers. More asthma and COPD patients preferred ELLIPTA over comparator inhalers..

Gepubliceerd: NPJ Prim Care Respir Med 2017 Mar 23;27:17001
Impact factor: 2.793

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**22. Small pulmonary nodules in baseline and incidence screening rounds of low-dose CT lung cancer screening**
Walter JE, Heuvelmans MA, Oudkerk M

Currently, lung cancer screening by low-dose computed tomography (LDCT) is widely recommended for high-risk individuals by US guidelines, but there still is an ongoing debate concerning respective recommendations for European countries. Nevertheless, the available data regarding pulmonary nodules released by lung cancer screening studies could improve future screening guidelines, as well as the clinical practice of incidentally detected pulmonary nodules on routine CT scans. Most lung cancer screening trials present results for baseline and incidence screening rounds separately, clustering pulmonary nodules initially found at baseline screening and newly detected pulmonary nodules after baseline screening together. This approach does not appreciate possible differences among pulmonary nodules detected at baseline and firstly detected at incidence screening rounds and is heavily influenced by methodological differences of the respective screening trials. This review intends to create a basis for assessing non-calcified pulmonary nodules detected during LDCT lung cancer screening in a more clinical relevant manner. The aim is to present data of non-calcified pulmonary baseline nodules and new non-calcified pulmonary incident nodules without clustering them together, thereby also simplifying translation to the clinical practice of incidentally detected pulmonary nodules. Small pulmonary nodules newly detected at incidence screening rounds of LDCT lung cancer screening may possess a greater lung cancer probability than pulmonary baseline nodules at a smaller size, which is essential for the development of new guidelines.

Gepubliceerd: Transl Lung Cancer Res 2017 Feb;6(1):42-51
Impact factor: 0

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**23. Stable State Proadrenomedullin Level in COPD Patients: A Validation Study**
Zuur-Telgen M, VanderValk P, van der Palen J, Kerstjens HA, Brusse-Keizer M

In patients with stable COPD, proadrenomedullin (MR-proADM) has been shown to be a good predictor for mortality. This study aims to provide an external validation of earlier observed cut-off values used by Zuur-Telgen et al. and Stolz.et al. in COPD

patients in stable state and at hospitalization for an acute exacerbation of COPD (AECOPD). From the COMIC cohort study we included 545 COPD patients with a blood sample obtained in stable state (n = 490) and/or at hospitalization for an AECOPD (n = 101). Time to death was compared between patients with MR-proADM cut-off scores 0.71 and 0.75 nmol/L for stable state or 0.79 and 0.84 nmol/l for AECOPD. The predictive value of MR-proADM for survival was represented by the C statistic. Risk ratios were corrected for sex, age, BMI, presence of heart failure, and GOLD stage. Patients above the cut-off of 0.75 nmol/l had a 2-fold higher risk of dying than patient below this cut-off (95% CI: 1.20-3.41). The cut-off of 0.71 nmol/l showed only a borderline significantly higher risk of 1.67 (95% CI: 0.98-2.85). The corrected odds ratios for one-year mortality were 3.15 (95% CI 1.15-8.64) and 3.70 (95% CI 1.18-11.6) in patients with MR-proADM levels above versus below the cut-off of respectively 0.75 and 0.71 nmol/l measured in stable state. MR-proADM levels in samples at hospitalization for an AECOPD were not predictive for mortality in this validation cohort. MR-proADM in stable state is a powerful predictor for mortality.

Gepubliceerd: COPD 2017 Apr;14(2):219-27
Impact factor: 2.576

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**24. Is pulmonary diffusion capacity for nitric oxide (DL,NO) likely to become a routine pulmonary function test?**
Steenbruggen I, de Jongh FH

DL,CO measurements are often used to evaluate and monitor lung diseases as well as cardiovascular diseases. Whether the combination of DL,CO and DL,NO will improve the management of cardiovascular diseases needs to be investigated. It is hoped that the standardization of the DL,NO measurement will facilitate research. Scientific evidence that DL,NO can provide more accurate information than DL,CO alone, can take away the barriers that prevents DL,NO to become a routine test in pulmonology.

Gepubliceerd: Respir Physiol Neurobiol 2017 Jul;241:7-8
Impact factor: 1.660

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Totale impact factor: 109.861
Gemiddelde impact factor: 4.578

Aantal artikelen 1e, 2e of laatste auteur: 14
Totale impact factor: 37.014

Gemiddelde impact factor: 2.644

# MDL

**1. Vascular disorders of the gastrointestinal tract**
Acosta S, Kolkman JJ

Gepubliceerd: Best Pract Res Clin Gastroenterol 2017 Feb;31(1):1-2
Impact factor: 3.762

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**2. Editor's Choice - Management of the Diseases of Mesenteric Arteries and Veins: Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS)**
Bjorck M, Koelemay M, Acosta S, Bastos Goncalves F, Kolbel T, Kolkman JJ, Lees T, Lefevre JH, Menyhei G, Oderich G, Kolh P, de Borst GJ, Chakfe N, Debus S, Hinchliffe R, Kakkos S, Koncar I, Sanddal Lindholt J, Vega de Ceniga M, Vermassen F, Verzini F, Geelkerken B, Gloviczki P, Huber T, Naylor R

Gepubliceerd: Eur J Vasc Endovasc Surg 2017 Apr;53(4):460-510
Impact factor: 4.061

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**3. Chronic Mesenteric Ischemia: when and how to intervene on patients with celiac/SMA stenosis**
Blauw J, Bulut T, Eenhoorn P, Beuk RJ, Brusse-Keizer M, Kolkman J, Geelkerken RH

Studies that compared open surgical mesenteric artery repair (OSMAR) with percutaneous mesenteric artery stenting (PMAS) in patients with chronic mesenteric ischemia (CMI) are based on merely older studies in which only a minority of patients received PMAS. This does not reflect the current PMAS-first choice treatment paradigm. This article focused on the present opinions and changes in outcomes of OSMAR for CMI in the era of preferred use of PMAS. Patients who received OSMAR for CMI from 1997 until 2014 in a tertiary referral centre for chronic mesenteric ischemia were included in this report. Patients were divided into two groups, the historical OSMAR preferred group and present PMAS preferred group. Patient characteristics, SVS comorbidity severity score, clinical presentation and number of diseased mesenteric arteries were not significantly changed after the widespread introduction of PMAS. In the present PMAS first era there were trends of less open surgical mesenteric artery multi-vessel repair, less antegrade situated bypasses, decreased clinical success but improved survival after OSMAR. Elective OSMAR should only be used in patients with substantial physiologic reserve and who have

unfavourable mesenteric lesions, failed PMAS or multiple recurrences of in-stent stenosis/occlusion. PMAS in CMI patients is evolved from 'bridge to surgery' to nowadays first choice treatment and "bridge to repeated PMAS" in almost all patients with CMI**.**

Gepubliceerd: J Cardiovasc Surg (Torino) 2017;58(2):321-8
Impact factor: 1.632

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**4. Long-Term Results of Endovascular Treatment of Atherosclerotic Stenoses or Occlusions of the Coeliac and Superior Mesenteric Artery in Patients With Mesenteric Ischaemia**
Bulut T, Oosterhof-Berktas R, Geelkerken RH, Brusse-Keizer M, Stassen EJ, Kolkman JJ

**Introduction:** Over the past decade, primary percutaneous mesenteric artery stenting (PMAS) has become an alternative to open revascularisation for treatment of mesenteric ischaemia. Institutes have presented favourable short-term outcomes after PMAS, but there is a lack of data on long-term stent patency.
**Methods:** One hundred and forty-one patients treated by PMAS for acute and chronic mesenteric ischaemia over an 8 year period were studied. Anatomical success was assessed by duplex ultrasound and/or CT angiography. A stenosis >/=70% was considered to be a failure.
**Results:** Eighty-six coeliac arteries (CA) and 99 superior mesenteric arteries (SMA) were treated with PMAS in 141 patients. Nine CAs (10%) and 30 SMAs (30%) were occluded at the time of treatment. Median follow-up was 32 months (IQR 20-46). The overall primary patency rate at 12 and 60 months was 77.0% and 45.0%. The overall primary assisted patency rate was 90.3% and 69.8%. Overall secondary patency was 98.3% and 93.6%.
**Conclusion:** This study shows excellent long-term secondary patencies after PMAS, comparable with published data on long-term patencies after open surgical revascularisation**.**

Gepubliceerd: Eur J Vasc Endovasc Surg 2017 Feb 18;53(4):583-90
Impact factor: 4.061

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**5. Diagnostic Accuracy of the Combination of Clinical Symptoms and CT or MR Angiography in Patients With Chronic Gastrointestinal Ischemia**
Harki J, Vergouwe Y, Spoor JA, Mensink PB, Bruno MJ, van Noord D, Kuipers EJ, Tjwa ETTL

**Background:** No golden diagnostic standard is available to diagnose chronic gastrointestinal ischemia (CGI). GOALS: We aimed to establish an accurate prediction model for CGI, based on clinical symptoms and radiologic evaluation of the amount of stenosis in the celiac artery (CA) and superior mesenteric artery (SMA) by means of computed tomography-angiography or magnetic resonance (MR)-angiography.
**Study:** We prospectively included 436 consecutive patients with clinical suspicion of CGI in a tertiary referral center. Predictors for CGI were obtained by comparing clinical parameters to the diagnosis of CGI. Multivariable logistic regression was used to combine the strongest predictors in a model. A score chart based on the prediction model was provided to calculate the risk of CGI.
**Results:** CGI was present in 171/436 (39%) patients (67 y; range, 54 to 74 y; 27% male). Strongest predictors for CGI were female gender [odds ratio (OR)=1.44; 95% confidence interval (CI), 0.85-2.43], weight loss (OR=1.63, 95% CI, 0.98-2.72), concomitant cardiovascular disease (OR=1.70, 95% CI, 1.04-2.78), duration of symptoms (OR=0.88, 95% CI, 0.79-0.99), and stenosis of CA and SMA (50% to 70% stenosis CA: OR=1.33, 95% CI, 0.56-3.19; >70% stenosis CA: OR=5.79, 95% CI, 3.42-9.81; 50% to 70% stenosis SMA: OR=3.21, 95% CI, 0.81-12.74; >70% stenosis SMA: OR=4.39, 95% CI, 2.30-8.41). A model based on clinical symptoms alone showed limited discriminative ability for diagnosing CGI (c-statistic 0.62). Adding radiologic imaging of the mesenteric arteries improved the discriminative ability (c-statistic 0.79).
**Conclusions:** Clinical symptoms alone are insufficient to predict the risk of CGI. Radiologic evaluation of the mesenteric arteries is essential. This tool may be useful for clinicians to assess the risk of CGI and to decide whether further diagnostic work-up for CGI is needed**.**

Gepubliceerd: J Clin Gastroenterol 2017 Jul;51(6):e39-e47
Impact factor: 3.328

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**6. Diagnosis and treatment of chronic mesenteric ischemia: An update**
Kolkman JJ, Geelkerken RH

Although the prevalence of mesenteric artery stenoses (MAS) is high, symptomatic chronic mesenteric ischemia (CMI) is rare. The collateral network in the mesenteric circulation, a remnant of the extensive embryonal vascular network, serves to prevent most cases of ischemia. This explains the high incidence of MAS and relative rarity of cases of CMI. The number of affected vessels is the major determinant in CMI development. Most subjects with single vessel mesenteric stenosis do not develop

ischemic complaints. Our experience is that most subjects with CA and SMA stenoses with abdominal complaints have CMI. A special mention should be made on patients with median arcuate ligament compression (MALS). There is ongoing debate whether the intermittent compression, caused by respiration movement, can cause ischemic complaints. The arguments pro and con treatment of MALS will be discussed. The clinical presentation of CMI consists of postprandial pain, weight loss, and an adapted eating pattern caused by fear of eating. In end-stage disease more continuous pain, diarrhea or a dyspepsia-like presentation can be observed. Workup of patients suspected for CMI consists of three elements: the anamnesis, the vascular anatomy and proof of ischemia. The main modalities to establish mesenteric vessel patency are duplex ultrasound, CT angiography or MR angiography. Assessing actual ischemia is still challenging, with only tonometry and visual light spectroscopy as tested candidates. Treatment consists of limiting metabolic demand, treatment of the atherosclerotic process and endovascular or operative revascularisation. Metabolic demand can be reduced by using smaller and more frequent meals, proton pump inhibition. Treatment of the atherosclerotic process consists of cessation of smoking, treatment of dyslipidemia, hypertension, hyperglycaemia, and medication with trombocyte aggregation inhibitors**.**

Gepubliceerd: Best Pract Res Clin Gastroenterol 2017 Feb;31(1):49-57
Impact factor: 3.762

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**7. Colon ischemia: Right-sided colon involvement has a different presentation, etiology and worse outcome. A large retrospective cohort study in histology proven patients**

Ten Heggeler LB, van Dam LJ, Bijlsma A, Visschedijk MC, Geelkerken RH, Meijssen MA, Kolkman JJ

**Background:** Colon ischemia (CI), is generally considered a non-occlusive mesenteric ischemia disorder that usually runs a benign course, but right-sided involvement (RCI) has been associated with worse outcome. The poor outcome of RCI has been associated with comorbidity, but more recently also with occlusions of the mesenteric arteries. We performed a retrospective analysis of a large cohort of CI-patients to assess differences in presentation, etiology, and comorbidity between right-sided colon ischemia (RCI) and non-right-sided colon ischemia (NRCI), and their relation to outcome.
**Methods:** We performed a retrospective cohort study in two centers from 2000 to 2011 for CI and analyzed clinical presentation, etiology, treatment and outcome. Diagnosis was based on full colonoscopy and/or surgical findings and confirmed by histopathology.

**Results:** 239 patients were included (mean age 69, 52% female). RCI was found in 48% and NRCI in 52%. Patients with NRCI presented more often with rectal bleeding (87% vs. 45%; p<0.001). In RCI more nausea (58% vs. 39%; p=0.013), weight loss (56% vs. 19%; p<0.001), paralytic ileus (32% vs. 18%; p=0.018) and peritoneal signs (27% vs. 7%; p<0.001) was observed compared to NRCI. The cause of CI was more often idiopathic in NRCI (46% vs. 26%; p=0.002); an occlusive cause was seen more often in RCI (26.3 vs 2.4%, p<0.0001). RCI patients had longer hospital stay (15 vs. 8 days, p<0.001), need for surgery (61% vs. 34%, p<0.001), and trend toward higher 30-day in-hospital mortality (20% vs. 12%, p=0.084).
**Conclusions:** RCI ischemia has different etiology, presentation, and outcome. The series shows a high proportion of - treatable - vessel occlusion. It reinforces the advice to perform CT angiography in RCI as means to improve its poor outcome**.**

Gepubliceerd: Best Pract Res Clin Gastroenterol 2017 Feb;31(1):111-7
Impact factor: 3.762

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**8. Functional testing in the diagnosis of chronic mesenteric ischemia**
van Noord D, Kolkman JJ

Chronic mesenteric ischemia (CMI) results from insufficient oxygen delivery or utilization to meet metabolic demand. Two main mechanisms may lead to mesenteric ischemia: occlusion in the arteries or veins of the gastrointestinal tract, or reduced blood flow from shock states or increased intra-abdominal pressure, so-called non-occlusive mesenteric ischemia. Severe stenoses in the three main mesenteric vessels as demonstrated with CT-angiography or MR-angiography are sufficient to proof mesenteric ischemia, for example in patients who present with weight loss, postprandial pain and diarrhea. Still in many clinical situations mesenteric ischemia is only one of many possible explanations. Especially in patients with a single vessel stenosis in the celiac artery or superior mesenteric artery with postprandial pain, mesenteric ischemia remains a diagnosis of probability or assumption without functional proof of actual ischemia. This review is aimed to provide an overview of all past, present and future ways to functionally proof CMI**.**

Gepubliceerd: Best Pract Res Clin Gastroenterol 2017 Feb;31(1):59-68
Impact factor: 3.762

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**9. Clinical significance of mesenteric arterial collateral circulation in patients with celiac artery compression syndrome**

van Petersen AS, Kolkman JJ, Gerrits DG, van der Palen J, Zeebregts CJ, Geelkerken RH

**Objective:** Although extensive collateral arterial circulation will prevent ischemia in most patients with stenosis of a single mesenteric artery, mesenteric ischemia may occur in these patients, for example, in patients with celiac artery compression syndrome (CACS). Variation in the extent of collateral circulation may explain the difference in clinical symptoms and variability in response to therapy; however, evidence is lacking. The objective of the study was to classify the presence of mesenteric arterial collateral circulation in patients with CACS and to evaluate the relation with clinical improvement after treatment.
**Methods:** Collateral mesenteric circulation was classified on the basis of angiographic findings. Collaterals were categorized in three groups: no visible collaterals (grade 0), collaterals seen on selective angiography only (grade 1), and collaterals visible on nonselective angiography (grade 2). Surgical release of the celiac artery in patients with suspected CACS was performed by arcuate ligament release. Clinical success after surgical revascularization was defined as an improvement in abdominal pain.
**Results:** Between 2002 and 2013, there were 135 consecutive patients with suspected CACS who were operated on. In 129 patients, preoperative angiograms allowed classification of collateral circulation. Primary assisted anatomic success was 93% (120/129). In patients with grade 0 collaterals, clinical success was 81% (39 of 48 patients); with grade 1 collaterals, 89% (25 of 28 patients); and with grade 2 collaterals, 52% (23 of 44 patients; $P < .001$).
**Conclusions:** Patients with CACS and with extensive collateral mesenteric arterial circulation are less likely to benefit from arcuate ligament release than are patients without this type of collateral circulation. The classification of the extent of mesenteric collateral circulation may predict and guide shared decision-making in patients with CACS.

Gepubliceerd: J Vasc Surg 2017 May;65(5):1366-74
Impact factor: 3.536

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**10. Higher quality of life after metal stent placement compared with plastic stent placement for malignant extrahepatic bile duct obstruction: 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, Steyerberg EW, May AM, Leenders M, Hirdes MM, Vleggaar FP, Siersema PD

**Objective:** For palliation of extrahepatic bile duct obstruction, self-expandable metal stents (SEMS) are superior to plastic stents in terms of stent patency and occurrence of stent dysfunction. We assessed health-related quality of life (HRQoL) after stent placement to investigate whether this also results in a difference in HRQoL between patients treated with a plastic stent or SEMS.
**Patients and methods:** This randomized multicenter trial included 219 patients who were randomized to receive plastic stent (n=73) or SEMS [uncovered (n=75) and covered (n=71); n=146] placement. HRQoL was assessed with two general questionnaires (EQ-5D-3L and QLQ-C30) and one disease-specific questionnaire (PAN-26). Scores were analyzed using linear mixed model regression and included all patients with baseline and at least one follow-up measurement.
**Results:** HRQoL data were available in 140 of 219 patients (64%); 71 patients (32%) declined participation and in eight patients (4%) only baseline questionnaires were available. On the QLQ-C30, the interaction between follow-up time and type of stent was significantly different on two of five functional scales [physical functioning (P=0.004) and emotional functioning (P=0.01)] in favor of patients with a SEMS. In addition, patients with SEMS reported significantly less frequent symptoms of fatigue (P=0.01), loss of appetite (P=0.02), and nausea and vomiting (0.04) over time. The EQ-VAS score decreased with time in both treatment groups, indicating a statistically significant decrease in HRQoL over time.
**Conclusion:** In patients with inoperable malignant extrahepatic bile duct obstruction, SEMS placement results in better scores for general and disease-specific HRQoL over time compared with plastic stent placement**.**

Gepubliceerd: Eur J Gastroenterol Hepatol 2017 Feb;29(2):231-7
Impact factor: 1.968

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Totale impact factor: 33.634
Gemiddelde impact factor: 3.363

Aantal artikelen 1e, 2e of laatste auteur: 6
Totale impact factor: 22.645
Gemiddelde impact factor: 3.774

# Medical School Twente

**1. The predictive value of an adjusted COPD assessment test score on the risk of respiratory-related hospitalizations in severe COPD patients**
Barton CA, Bassett KL, Buckman J, Effing TW, Frith PA, van der Palen J, Sloots JM

We evaluated whether a chronic obstructive pulmonary disease (COPD) assessment test (CAT) with adjusted weights for the CAT items could better predict future respiratory-related hospitalizations than the original CAT. Two focus groups (respiratory nurses and physicians) generated two adjusted CAT algorithms. Two multivariate logistic regression models for infrequent (</=1/year) versus frequent (>1/year) future respiratory-related hospitalizations were defined: one with the adjusted CAT score that correlated best with future hospitalizations and one with the original CAT score. Patient characteristics related to future hospitalizations ( p </= 0.2) were also entered. Eighty-two COPD patients were included. The CAT algorithm derived from the nurse focus group was a borderline significant predictor of hospitalization risk (odds ratio (OR): 1.07; 95% confidence interval (CI): 1.00-1.14; p = 0.050) in a model that also included hospitalization frequency in the previous year (OR: 3.98; 95% CI: 1.30-12.16; p = 0.016) and anticholinergic risk score (OR: 3.08; 95% CI: 0.87-10.89; p = 0.081). Presence of ischemic heart disease and/or heart failure appeared 'protective' (OR: 0.17; 95% CI: 0.05-0.62; p = 0.007). The original CAT score was not significantly associated with hospitalization risk. In conclusion, as a predictor of respiratory-related hospitalizations, an adjusted CAT score was marginally significant (although the original CAT score was not). 'Previous respiratory-related hospitalizations' was the strongest factor in this equation.

Gepubliceerd: Chron Respir Dis 2017 Feb;14(1):72-84
Impact factor: 1.818

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**2. Carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy**
Berghuis B, van der Palen J, de Haan GJ, Lindhout D, Koeleman BPC, Sander JW

**Objective:** To ascertain possible determinants of carbamazepine (CBZ)- and oxcarbazepine (OXC)-induced hyponatremia in a large cohort of people with epilepsy.
**Methods:** We collected data on serum sodium levels in people with epilepsy who were attending a tertiary epilepsy center while on treatment with CBZ or OXC. We defined hyponatremia as Na+ </=134 mEq/L and severe hyponatremia as Na+ </=128 mEq/L.

**Results:** We identified 1,782 people who had used CBZ (n = 1,424) or OXC (n = 358), of whom 50 were treated with both drugs. Data on sodium level measurements were available in 1,132 on CBZ and in 289 on OXC. Hyponatremia occurred in 26% of those taking CBZ and 46% of those taking OXC. This was severe in 7% in the CBZ group and 22% in the OXC group. Hyponatremia was symptomatic in 48% and led to admissions in 3%. Age over 40 years, high serum levels of CBZ and OXC, and concomitant use of other antiepileptic drugs were the main risk factors for hyponatremia in both treatment groups. Female patients on OXC were at a higher risk than male patients of hyponatremia. The risk of hyponatremia on CBZ was significantly associated with the risk of hyponatremia on OXC within a subgroup that used both drugs consecutively.
**Significance:** Hyponatremia is a common problem in people taking CBZ or OXC. Regular ascertainment of sodium levels in those taking either drug is recommended and results should be acted on.

Gepubliceerd: Epilepsia 2017 Jul;58(7):1227-33
Impact factor: 5.295

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**3. Chronic Mesenteric Ischemia: when and how to intervene on patients with celiac/SMA stenosis**
Blauw J, Bulut T, Eenhoorn P, Beuk RJ, Brusse-Keizer M, Kolkman J, Geelkerken RH

Studies that compared open surgical mesenteric artery repair (OSMAR) with percutaneous mesenteric artery stenting (PMAS) in patients with chronic mesenteric ischemia (CMI) are based on merely older studies in which only a minority of patients received PMAS. This does not reflect the current PMAS-first choice treatment paradigm. This article focused on the present opinions and changes in outcomes of OSMAR for CMI in the era of preferred use of PMAS. Patients who received OSMAR for CMI from 1997 until 2014 in a tertiary referral centre for chronic mesenteric ischemia were included in this report. Patients were divided into two groups, the historical OSMAR preferred group and present PMAS preferred group. Patient characteristics, SVS comorbidity severity score, clinical presentation and number of diseased mesenteric arteries were not significantly changed after the widespread introduction of PMAS. In the present PMAS first era there were trends of less open surgical mesenteric artery multi-vessel repair, less antegrade situated bypasses, decreased clinical success but improved survival after OSMAR. Elective OSMAR should only be used in patients with substantial physiologic reserve and who have unfavourable mesenteric lesions, failed PMAS or multiple recurrences of in-stent stenosis/occlusion. PMAS in CMI patients is evolved from 'bridge to surgery' to

nowadays first choice treatment and "bridge to repeated PMAS" in almost all patients with CMI.

Gepubliceerd: J Cardiovasc Surg (Torino) 2017;58(2):321-8
Impact factor: 1.632

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**4. Endoscopic third ventriculostomy and repeat endoscopic third ventriculostomy in pediatric patients: the Dutch experience**
Breimer GE, Dammers R, Woerdeman PA, Buis DR, Delye H, Brusse-Keizer M, Hoving EW

**Objective:** After endoscopic third ventriculostomy (ETV), some patients develop recurrent symptoms of hydrocephalus. The optimal treatment for these patients is not clear: repeat ETV (re-ETV) or CSF shunting. The goals of the study were to assess the effectiveness of re-ETV relative to initial ETV in pediatric patients and validate the ETV success score (ETVSS) for re-ETV.
**Methods:** Retrospective data of 624 ETV and 93 re-ETV procedures were collected from 6 neurosurgical centers in the Netherlands (1998-2015). Multivariable Cox proportional hazards modeling was used to provide an adjusted estimate of the hazard ratio for re-ETV failure relative to ETV failure. The correlation coefficient between ETVSS and the chance of re-ETV success was calculated using Kendall's tau coefficient. Model discrimination was quantified using the c-statistic. The effects of intraoperative findings and management on re-ETV success were also analyzed.
**Results:** The hazard ratio for re-ETV failure relative to ETV failure was 1.23 (95% CI 0.90-1.69; p = 0.20). At 6 months, the success rates for both ETV and re-ETV were 68%. ETVSS was significantly related to the chances of re-ETV success (tau = 0.37; 95% bias corrected and accelerated CI 0.21-0.52; p < 0.001). The c-statistic was 0.74 (95% CI 0.64-0.85). The presence of prepontine arachnoid membranes and use of an external ventricular drain (EVD) were negatively associated with treatment success, with ORs of 4.0 (95% CI 1.5-10.5) and 9.7 (95% CI 3.4-27.8), respectively.
**Conclusions:** Re-ETV seems to be as safe and effective as initial ETV. ETVSS adequately predicts the chance of successful re-ETV. The presence of prepontine arachnoid membranes and the use of EVD negatively influence the chance of success.

Gepubliceerd: J Neurosurg Pediatr 2017 Oct;20(4):314-23
Impact factor: 2.170

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**5. Comparing the 2007 and 2011 GOLD Classifications as Predictors of all-Cause Mortality and Morbidity in COPD**
Brusse-Keizer M, Klatte M, Zuur-Telgen M, Koehorst-Ter Huurne K, van der Palen J, VanderValk P

To better classify patients with chronic obstructive pulmonary disease (COPD) for prognostic purposes and to tailor treatment, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 classification was revised in 2011. The primary aim of the current data analyses was to evaluate the accuracy of the GOLD 2007 and 2011 GOLD classifications to predict all-cause mortality and morbidity in a well-described COPD cohort. The prognostic values of both GOLD classifications, expressed as the C-statistic, were assessed in the Cohort of Mortality and Inflammation in COPD (COMIC) study of 795 COPD patients, with a follow-up of 3 years. Outcomes were all-cause mortality and morbidity. Morbidity was defined as time until first COPD-related hospitalisation and time until first community-acquired pneumonia (CAP). The prognostic value of the GOLD 2011 classification was compared between symptom classification based on the modified Medical Research Council (mMRC) score and the Clinical COPD Questionnaire (CCQ) scores with two different thresholds. Although the GOLD 2011 CCQ classification had the highest accuracy to predict mortality and morbidity in our study, the C-statistics differed only numerically. Furthermore, our study showed that the instrument used to determine the level of symptoms in the GOLD 2011 classification has not only important consequences on the mortality prognosis, but also affects the morbidity prognosis in COPD. Therefore, patients' estimated prognosis could alter when different types of tools are used to evaluate the prognosis.

Gepubliceerd: COPD 2017 Feb;14(1):7-14
Impact factor: 2.576

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**6. Long-Term Results of Endovascular Treatment of Atherosclerotic Stenoses or Occlusions of the Coeliac and Superior Mesenteric Artery in Patients With Mesenteric Ischaemia**
Bulut T, Oosterhof-Berktas R, Geelkerken RH, Brusse-Keizer M, Stassen EJ, Kolkman JJ

**Introduction:** Over the past decade, primary percutaneous mesenteric artery stenting (PMAS) has become an alternative to open revascularisation for treatment of mesenteric ischaemia. Institutes have presented favourable short-term outcomes after PMAS, but there is a lack of data on long-term stent patency.

**Methods:** One hundred and forty-one patients treated by PMAS for acute and chronic mesenteric ischaemia over an 8 year period were studied. Anatomical success was assessed by duplex ultrasound and/or CT angiography. A stenosis >/=70% was considered to be a failure.
**Results:** Eighty-six coeliac arteries (CA) and 99 superior mesenteric arteries (SMA) were treated with PMAS in 141 patients. Nine CAs (10%) and 30 SMAs (30%) were occluded at the time of treatment. Median follow-up was 32 months (IQR 20-46). The overall primary patency rate at 12 and 60 months was 77.0% and 45.0%. The overall primary assisted patency rate was 90.3% and 69.8%. Overall secondary patency was 98.3% and 93.6%.
**Conclusion:** This study shows excellent long-term secondary patencies after PMAS, comparable with published data on long-term patencies after open surgical revascularisation.

Gepubliceerd: Eur J Vasc Endovasc Surg 2017 Feb 18;53(4):583-90
Impact factor: 4.061

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**7. Device errors in asthma and COPD: systematic literature review and meta-analysis**
Chrystyn H, van der Palen J, Sharma R, Barnes N, Delafont B, Mahajan A, Thomas M

Inhaler device errors are common and may impact the effectiveness of the delivered drug. There is a paucity of up-to-date systematic reviews (SRs) or meta-analyses (MAs) of device errors in asthma and chronic obstructive pulmonary disease (COPD) patients. This SR and MA provides an estimate of overall error rates (both critical and non-critical) by device type and evaluates factors associated with inhaler misuse. The following databases from inception to July 23, 2014 (Embase(R), MEDLINE(R), MEDLINE(R) In-Process and CENTRAL) were searched, using predefined search terms. Studies in adult males and females with asthma or COPD, reporting at least one overall or critical error, using metered dose inhalers and dry powder inhalers were included. Random-effect MAs were performed to estimate device error rates and to compare pairs of devices. Overall and critical error rates were high across all devices, ranging from 50-100% and 14-92%, respectively. However, between-study heterogeneity was also generally >90% (I-squared statistic), indicating large variability between studies. A trend towards higher error rates with assessments comprising a larger number of steps was observed; however no consistent pattern was identified. This SR and MA highlights the relatively limited body of evidence assessing device errors and the lack of standardised checklists. There is currently insufficient evidence to determine differences in error rates between different inhaler devices and their

impact on clinical outcomes. A key step in improving our knowledge on this topic would be the development of standardised checklists for each device.
**Chronic lung diseases: call to standardise research into inhaler device errors:** Researchers should adopt a standardised approach to investigate the incorrect use of inhalers and its associated clinical implications. Henry Chrystyn at Plymouth University, together with scientists across the UK and the Netherlands, conducted a review of research related to inhaled medication errors made by patients with asthma or chronic obstructive pulmonary disease. It is widely acknowledged that many patients with lung conditions don't use their inhaler devices correctly, which affects drug effectiveness and disease control. While Chrystyn's team found high critical error rates reported across all devices, their meta-analysis and systematic review highlighted significant gaps in knowledge regarding different inhalers and associated error rates, and how these affect clinical outcomes. The researchers call for in-depth studies into device use, alongside standardised checklists and definitions for such studies to use to ensure consistency.

Gepubliceerd: NPJ Prim Care Respir Med 2017 Apr 3;27(1):22
Impact factor: 2.793

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**8. The TL,NO /TL,CO ratio cannot be used to exclude pulmonary embolism**
Fabius TM, Eijsvogel MM, van der Lee I, Brusse-Keizer M, de Jongh FH

**Background:** The existing screening modalities for pulmonary embolism (PE), such as D-dimer and clinical prediction rules, have low positive predictive values. With its capability to indicate pulmonary vascular abnormalities, the ratio of the transfer factor of the lungs for nitric oxide and the transfer factor of the lungs for carbon monoxide (TL,NO /TL,CO ) might be an additional discriminating parameter.
**Methods:** Carbon monoxide/Nitric oxide diffusion measurements were performed on unselected patients seen on the emergency department for which due to suspected PE a computed tomography pulmonary angiogram (CTPA) was ordered.
**Results:** A total of 28 patients were included, PE was found in 12 on CTPA. Median TL,NO /TL,CO ratio was 4.09 (interquartile range (IQR) 3.83-4.40) in the no PE group versus 4.00 (IQR 3.78-4.32) in the PE group (P = 0.959). Median alveolar volume was 77.1% of predicted in the no PE group versus 71.0% of predicted in the PE group (P = 0.353). Median TL,CO was 75.8% of predicted in the no PE group versus 68.8% of predicted in the PE group (P = 0.120). Median TL,NO was 69.3% of predicted in the no PE group versus 60.5% of predicted in the PE group (P = 0.078).
**Conclusion:** The presented data indicate that the TL,NO /TL,CO ratio cannot be used to exclude PE.

Gepubliceerd: Clin Physiol Funct Imaging 2017 Jul;37(4):400-4
Impact factor: 2.300

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**9. Concerns with beta2-agonists in pediatric asthma - a clinical perspective**
Kersten ET, Koppelman GH, Thio BJ

Beta2-adrenoreceptor agonists (beta2-agonists) are extensively used in the treatment of childhood asthma. However, there have been concerns regarding their adverse effects and safety. In 2005, the FDA commissioned a "Black Box Warning" communicating the potential for an increased risk for serious asthma exacerbations or asthma related deaths, with the regular use of LABAs. In a meta-analysis of controlled clinical trials, the incidence of severe adverse events appeared to be highest in the 4-11 year age group. Several mechanisms have been proposed regarding the risk of regular use of beta2-agonists, such as masking patients' perception of worsening asthma, desensitization and downregulation of the beta2-adrenoreceptor, pro-inflammatory effects of beta2-agonists, pharmacogenetic effects of beta2-adrenoreceptor polymorphisms and age related differences in pathophysiology of asthma. In this paper, we review beta2-receptor pharmacology, discuss the concerns regarding treatment with beta2-agonists in childhood asthma, and provide suggestions for clinical pediatric practice in the light of current literature.

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Impact factor: 2.214

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**10. Data analysis of electronic nose technology in lung cancer: generating prediction models by means of Aethena**
Kort S, Brusse-Keizer M, Gerritsen JW, van der Palen J

**Introduction:** Only 15% of lung cancer cases present with potentially curable disease. Therefore, there is much interest in a fast, non-invasive tool to detect lung cancer earlier. Exhaled breath analysis using electronic nose technology measures volatile organic compounds (VOCs) in exhaled breath that are associated with lung cancer.
**Methods:** The diagnostic accuracy of the Aeonose is currently being studied in a multi-centre, prospective study in 210 subjects suspected for lung cancer, where approximately half will have a confirmed diagnosis and the other half will have a rejected diagnosis of lung cancer. We will also include 100-150 healthy control subjects. The eNose Company (provider of the Aeonose) uses a software program, called Aethena, comprising pre-processing, data compression and neural networks to

handle big data analyses. Each individual exhaled breath measurement comprises a data matrix with thousands of conductivity values. This is followed by data compression using a Tucker3-like algorithm, resulting in a vector. Subsequently, model selection takes place after entering vectors with different presets in an artificial neural network to train and evaluate the results. Next, a 'judge model' is formed, which is a combination of models for optimizing performance. Finally, two types of cross-validation, being 'leave-10%-out' cross-validation and 'bagging', are used when recalculating the judge models. These judge models are subsequently used to classify new, blind measurements.
**Discussion:** Data analysis in eNose technology is principally based on generating prediction models that need to be validated internally and externally for eventual use in clinical practice. This paper describes the analysis of big data, captured by eNose technology in lung cancer. This is done by means of generating prediction models with Aethena, a data analysis program specifically developed for analysing VOC data.

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Impact factor: 4.318

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**11. Decrease in Switches to 'Unsafe' Proton Pump Inhibitors After Communications About Interactions with Clopidogrel**
Kruik-Kolloffel WJ, van der Palen J, van Herk-Sukel MPP, Kruik HJ, Movig KLL

**Background:** In 2009 and 2010 medicines regulatory agencies published official safety statements regarding the concomitant use of proton pump inhibitors and clopidogrel. We wanted to investigate a change in prescription behaviour in prevalent gastroprotective drug users (2008-2011).
**Methods:** Data on drug use were retrieved from the Out-patient Pharmacy Database of the PHARMO Database Network. We used interrupted time series analyses (ITS) to estimate the impact of each safety statement on the number of gastroprotective drug switches around the start of clopidogrel and during clopidogrel use.
**Results:** After the first statement (June 2009), significantly fewer patients switched from another proton pump inhibitor to (es)omeprazole (-14.9%; 95% CI -22.6 to -7.3) at the moment they started clopidogrel compared to the period prior to this statement. After the adjusted statement in February 2010, the switch percentage to (es)omeprazole decreased further (-4.5%; 95% CI -8.1 to -0.9). We observed a temporary increase in switches from proton pump inhibitors to histamine 2-receptor antagonists after the first statement; the decrease in the reverse switch was statistically significant (-23.0%; 95% CI -43.1 to -2.9).
**Conclusions:** With ITS, we were able to demonstrate a decrease in switches from other proton pump inhibitors to (es)omeprazole and an increase of the reverse switch

to almost 100%. We observed a partial and temporary switch to histamine 2-receptor antagonists. This effect of safety statements was shown for gastroprotective drug switches around the start of clopidogrel treatment.

Gepubliceerd: Clin Drug Investig 2017 Aug;37(8):787-94
Impact factor: 1.853

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**12. Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease**
Lenferink A, Brusse-Keizer M, van der Valk PD, Frith PA, Zwerink M, Monninkhof EM, van der Palen J, Effing TW

**Background:** Chronic Obstructive Pulmonary Disease (COPD) self-management interventions should be structured but personalised and often multi-component, with goals of motivating, engaging and supporting the patients to positively adapt their behaviour(s) and develop skills to better manage disease. Exacerbation action plans are considered to be a key component of COPD self-management interventions. Studies assessing these interventions show contradictory results. In this Cochrane Review, we compared the effectiveness of COPD self-management interventions that include action plans for acute exacerbations of COPD (AECOPD) with usual care.
**Objectives:** To evaluate the efficacy of COPD-specific self-management interventions that include an action plan for exacerbations of COPD compared with usual care in terms of health-related quality of life, respiratory-related hospital admissions and other health outcomes. SEARCH
**Methods:** We searched the Cochrane Airways Group Specialised Register of trials, trials registries, and the reference lists of included studies to May 2016.
**Selection criteria:** We included randomised controlled trials evaluating a self-management intervention for people with COPD published since 1995. To be eligible for inclusion, the self-management intervention included a written action plan for AECOPD and an iterative process between participant and healthcare provider(s) in which feedback was provided. We excluded disease management programmes classified as pulmonary rehabilitation or exercise classes offered in a hospital, at a rehabilitation centre, or in a community-based setting to avoid overlap with pulmonary rehabilitation as much as possible.
**Data collection and analysis:** Two review authors independently assessed trial quality and extracted data. We resolved disagreements by reaching consensus or by involving a third review author. Study authors were contacted to obtain additional information and missing outcome data where possible. When appropriate, study results were pooled using a random-effects modelling meta-analysis. The primary

outcomes of the review were health-related quality of life (HRQoL) and number of respiratory-related hospital admissions.

**Main results:** We included 22 studies that involved 3,854 participants with COPD. The studies compared the effectiveness of COPD self-management interventions that included an action plan for AECOPD with usual care. The follow-up time ranged from two to 24 months and the content of the interventions was diverse.Over 12 months, there was a statistically significant beneficial effect of self-management interventions with action plans on HRQoL, as measured by the St. George's Respiratory Questionnaire (SGRQ) total score, where a lower score represents better HRQoL. We found a mean difference from usual care of -2.69 points (95% CI -4.49 to -0.90; 1,582 participants; 10 studies; high-quality evidence). Intervention participants were at a statistically significant lower risk for at least one respiratory-related hospital admission compared with participants who received usual care (OR 0.69, 95% CI 0.51 to 0.94; 3,157 participants; 14 studies; moderate-quality evidence). The number needed to treat to prevent one respiratory-related hospital admission over one year was 12 (95% CI 7 to 69) for participants with high baseline risk and 17 (95% CI 11 to 93) for participants with low baseline risk (based on the seven studies with the highest and lowest baseline risk respectively).There was no statistically significant difference in the probability of at least one all-cause hospital admission in the self-management intervention group compared to the usual care group (OR 0.74, 95% CI 0.54 to 1.03; 2467 participants; 14 studies; moderate-quality evidence). Furthermore, we observed no statistically significant difference in the number of all-cause hospitalisation days, emergency department visits, General Practitioner visits, and dyspnoea scores as measured by the (modified) Medical Research Council questionnaire for self-management intervention participants compared to usual care participants. There was no statistically significant effect observed from self-management on the number of COPD exacerbations and no difference in all-cause mortality observed (RD 0.0019, 95% CI -0.0225 to 0.0263; 3296 participants; 16 studies; moderate-quality evidence). Exploratory analysis showed a very small, but significantly higher respiratory-related mortality rate in the self-management intervention group compared to the usual care group (RD 0.028, 95% CI 0.0049 to 0.0511; 1219 participants; 7 studies; very low-quality evidence).Subgroup analyses showed significant improvements in HRQoL in self-management interventions with a smoking cessation programme (MD -4.98, 95% CI -7.17 to -2.78) compared to studies without a smoking cessation programme (MD -1.33, 95% CI -2.94 to 0.27, test for subgroup differences: Chi(2) = 6.89, df = 1, P = 0.009, I(2) = 85.5%). The number of behavioural change techniques clusters integrated in the self-management intervention, the duration of the intervention and adaptation of maintenance medication as part of the action plan did not affect HRQoL. Subgroup analyses did not detect any potential variables to explain differences in respiratory-related hospital admissions among studies.

**Authors' conclusions:** Self-management interventions that include a COPD exacerbation action plan are associated with improvements in HRQoL, as measured with the SGRQ, and lower probability of respiratory-related hospital admissions. No excess all-cause mortality risk was observed, but exploratory analysis showed a small, but significantly higher respiratory-related mortality rate for self-management compared to usual care.For future studies, we would like to urge only using action plans together with self-management interventions that meet the requirements of the most recent COPD self-management intervention definition. To increase transparency, future study authors should provide more detailed information regarding interventions provided. This would help inform further subgroup analyses and increase the ability to provide stronger recommendations regarding effective self-management interventions that include action plans for AECOPD. For safety reasons, COPD self-management action plans should take into account comorbidities when used in the wider population of people with COPD who have comorbidities. Although we were unable to evaluate this strategy in this review, it can be expected to further increase the safety of self-management interventions. We also advise to involve Data and Safety Monitoring Boards for future COPD self-management studies.

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Impact factor: 6.264

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**13. Early or delayed provision of an ankle-foot orthosis in patients with acute and subacute stroke: a randomized controlled trial**
Nikamp CD, Buurke JH, van der Palen J, Hermens HJ, Rietman JS

**Objective:** (1) To study the effects of providing ankle-foot orthoses in subjects with (sub)acute stroke; and (2) to study whether the point in time at which an ankle-foot orthosis is provided post-stroke (early or delayed) influences these effects. DESIGN: Randomized controlled trial. SETTING: Rehabilitation centre.
**Subjects:** Unilateral hemiparetic stroke subjects with indication for use of an ankle-foot orthosis and maximal six weeks post-stroke.
**Interventions:** Subjects were randomly assigned to: early provision (at inclusion; Week 1) or delayed provision (eight weeks later; Week 9).
**Outcome measures:** 10-metre walk test, 6-minute walk test, Timed Up and Go Test, stairs test, Functional Ambulation Categories, Berg Balance Scale, Rivermead Mobility Index and Barthel Index; assessed in Weeks 1, 3, 9 and 11.
**Results:** A total of 33 subjects were randomized (16 early, 17 delayed). Positive effects of ankle-foot orthoses were found two weeks after provision, both when provided early (significant effects on all outcomes) or delayed (Berg Balance Scale p = 0.011, Functional Ambulation Categories p = 0.008, 6-minute walk test p = 0.005,

Timed Up and Go Test p = 0.028). Comparing effects after early and delayed provision showed that early provision resulted in increased levels of improvement on Berg Balance Scale (+5.1 points, p = 0.002), Barthel Index (+1.9 points, p = 0.002) and non-significant improvements on 10-metre walk test (+0.14 m/s, p = 0.093) and Timed Up and Go Test (-5.4 seconds, p = 0.087), compared with delayed provision. **Conclusions:** We found positive effects of providing ankle-foot orthoses in (sub)acute stroke subjects that had not used these orthoses before.

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Impact factor: 2.823

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**14. Six-month effects of early or delayed provision of an ankle-foot orthosis in patients with (sub)acute stroke: a randomized controlled trial**
Nikamp CD, Buurke JH, van der Palen J, Hermens HJ, Rietman JS

**Objective:** To study the six-month clinical effects of providing ankle-foot orthoses at different moments (early or delayed) in (sub)acute stroke; this is a follow-up to a published trial. DESIGN: Randomized controlled trial. SETTING: Rehabilitation centre.
**Subjects:** Unilateral hemiparetic stroke subjects maximal six weeks post-stroke with indication for ankle-foot orthosis use.
**Interventions:** Subjects were randomly assigned to early (at inclusion; week 1) or delayed provision (eight weeks later; week 9).
**Outcome measures:** Functional tests assessing balance and mobility were performed bi-weekly for 17 weeks and at week 26.
**Results:** In all, 33 subjects were randomized. No differences at week 26 were found between both groups for any of the outcome measures. However, results suggest that early provision leads to better outcomes in the first 11-13 weeks. Berg Balance Scale ( P = 0.006), Functional Ambulation Categories ( P = 0.033) and 6-minute walk test ( P < 0.001) showed significantly different patterns over time. Clinically relevant but statistically non-significant differences of 4-10 weeks in reaching independent walking with higher balance levels were found, favouring early provision.
**Conclusion:** No six-month differences in functional outcomes of providing ankle-foot orthoses at different moments in the early rehabilitation after stroke were found. Results suggest that there is a period of 11-13 weeks in which early provision may be beneficial, possibly resulting in early independent and safe walking. However, our study was underpowered. Further research including larger numbers of subjects is warranted.

Gepubliceerd: Clin Rehabil 2017 Dec;31(12):1616-24

Impact factor: 2.823

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**15. A randomized controlled trial on providing ankle-foot orthoses in patients with (sub-)acute stroke: Short-term kinematic and spatiotemporal effects and effects of timing**
Nikamp CDM, Hobbelink MSH, van der Palen J, Hermens HJ, Rietman JS, Buurke JH

Initial walking function is often limited after stroke, and regaining walking ability is an important goal in rehabilitation. Various compensatory movement strategies to ensure sufficient foot-clearance are reported. Ankle-foot orthoses (AFOs) are often prescribed to improve foot-clearance and may influence these strategies. However, research studying effects of actual AFO-provision early after stroke is limited. We conducted an explorative randomized controlled trial and aimed to study the short-term effects of AFO-provision on kinematic and spatiotemporal parameters in patients early after stroke. In addition, we studied whether timing of AFO-provision influenced these effects. Unilateral hemiparetic patients maximal six weeks post-stroke were randomly assigned to AFO-provision: early (at inclusion) or delayed (eight weeks later). Three-dimensional gait-analysis with and without AFO in randomized order was performed within two weeks after AFO-provision. Twenty subjects (8 early, 12 delayed) were analyzed. We found significant positive effects of AFO-provision for ankle dorsiflexion at initial contact, foot-off and during swing (-3.6 degrees (7.3) vs 3.0 degrees (3.9); 0.0 degrees (7.4) vs 5.2 degrees (3.7); and -6.1 degrees (7.8) vs 2.6 degrees (3.5), respectively), all p<0.001. No changes in knee, hip and pelvis angles were found after AFO-provision, except for knee (+2.3 degrees ) and hip flexion (+1.6 degrees ) at initial contact, p</=0.001. Significant effects of AFO-provision were found for cadence (+2.1 steps/min, p=0.026), stride duration (-0.08s, p=0.015) and single support duration (+1.0%, p=0.002). Early or delayed AFO-provision after stroke did not affect results. In conclusion, positive short-term effects of AFO-provision were found on ankle kinematics early after stroke. Timing of AFO-provision did not influence the results.
**Trial registration number:** NTR1930.

Gepubliceerd: Gait Posture 2017 Jun;55:15-22
Impact factor: 2.347

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**16. Use of three-dimensional computed tomography overlay for real-time cryoballoon ablation in atrial fibrillation reduces radiation dose and contrast dye**

Oude Velthuis B, Molenaar MMD, Reinhart Dorman HG, Stevenhagen JY, Scholten MF, van der Palen J, van Opstal JM

**Aims:** Cryoballoon pulmonary vein (PV) isolation in patients with atrial fibrillation has proven to be effective in short-term and long-term follow-up. To visualise the PV anatomy, pre-ablation contrast pulmonary venography is commonly performed. Three-dimensional (3D) computed tomography (CT) overlay is a new technique creating a live 3D image of the left atrium by integrating a previously obtained CT scan during fluoroscopy. To evaluate the benefits of 3D CT overlay during cryoballoon ablation, we studied the use of 3D CT overlay versus contrast pulmonary venography in a randomised fashion in patients with paroxysmal atrial fibrillation undergoing cryoballoon PV isolation.
**Methods and results:** Between October 2012 and June 2013, 30 patients accepted for PV isolation were randomised to cryoballoon PV isolation using either 3D CT overlay or contrast pulmonary venography. All patients underwent a pre-procedural cardiac CT for evaluation of the anatomy of the left atrium (LA) and the PVs. In the 3D CT overlay group, a 3D reconstruction of the LA and PVs was made. An overlay of the CT reconstruction was then projected over live fluoroscopy. Patients in the contrast pulmonary venography group received significantly more contrast agent (77.1 +/- 21.2 cc vs 40.1 +/- 17.6 cc, $p < 0.001$) and radiation (43.0 +/- 21.9 Gy.cm2 vs 28.41 +/- 11.7 Gy.cm2, $p = 0.04$) than subjects in the 3D CT overlay group. There was no difference in total procedure time, fluoroscopy time and the amount of cryoapplications between the two groups.
**Conclusion:** The use of 3D CT overlay decreases radiation and contrast dye exposure and can assist in guiding cryoballoon-based PV isolation.

Gepubliceerd: Neth Heart J 2017 Feb 15;25(6):388-93
Impact factor: 1.894

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**17. Item usage in a multidimensional computerized adaptive test (MCAT) measuring health-related quality of life**
Paap MCS, Kroeze KA, Terwee CB, van der Palen J, Veldkamp BP

**Purpose:** Examining item usage is an important step in evaluating the performance of a computerized adaptive test (CAT). We study item usage for a newly developed multidimensional CAT which draws items from three PROMIS domains, as well as a disease-specific one.
**Methods:** The multidimensional item bank used in the current study contained 194 items from four domains: the PROMIS domains fatigue, physical function, and ability to participate in social roles and activities, and a disease-specific domain (the COPD-

SIB). The item bank was calibrated using the multidimensional graded response model and data of 795 patients with chronic obstructive pulmonary disease. To evaluate the item usage rates of all individual items in our item bank, CAT simulations were performed on responses generated based on a multivariate uniform distribution. The outcome variables included active bank size and item overuse (usage rate larger than the expected item usage rate).
**Results:** For average theta-values, the overall active bank size was 9-10%; this number quickly increased as theta-values became more extreme. For values of -2 and +2, the overall active bank size equaled 39-40%. There was 78% overlap between overused items and active bank size for average theta-values. For more extreme theta-values, the overused items made up a much smaller part of the active bank size: here the overlap was only 35%.
**Conclusions:** Our results strengthen the claim that relatively short item banks may suffice when using polytomous items (and no content constraints/exposure control mechanisms), especially when using MCAT.

Gepubliceerd: Qual Life Res 2017 Jun 23;26(11):2909-18
Impact factor: 2.344

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**18. Treatment dropout in web-based cognitive behavioral therapy for patients with eating disorders**
Ter Huurne ED, Postel MG, de Haan HA, van der Palen J, de Jong CA

Treatment dropout is an important concern in eating disorder treatments as it has negative implications for patients' outcome, clinicians' motivation, and research studies. Our main objective was to conduct an exploratory study on treatment dropout in a two-part web-based cognitive behavioral therapy with asynchronous therapeutic support. The analysis included 205 female patients with eating disorders. Reasons for dropout, treatment experiences, and predictors of dropout were analyzed. Overall treatment dropout was 37.6%, with 18.5% early dropout (before or during treatment part 1) and 19.0% late dropout (after part 1 or during part 2). Almost half of the participants identified personal circumstances as reason for dropout. The other participants mostly reported reasons related to the online delivery or treatment protocol. Predictors of early dropout included reporting less vigor and smoking at baseline and a longer average duration per completed treatment module of part 1. Late dropout was predicted by reporting less vigor at baseline and uncertainty about recommendation of the treatment to others after completion of treatment part 1. Generally, the web-based treatment and online therapeutic support were evaluated positively, although dropouts rated the treatment as significantly less helpful and effective than completers did.

Gepubliceerd: Psychiatry Res 2017 Jan;247:182-93
Impact factor: 2.466

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**19. A randomised open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices**

van der Palen J, Thomas M, Chrystyn H, Sharma RK, van der Valk PD, Goosens M, Wilkinson T, Stonham C, Chauhan AJ, Imber V, Zhu CQ, Svedsater H, Barnes NC

Errors in the use of different inhalers were investigated in patients naive to the devices under investigation in a multicentre, single-visit, randomised, open-label, cross-over study. Patients with chronic obstructive pulmonary disease (COPD) or asthma were assigned to ELLIPTA vs DISKUS (Accuhaler), metered-dose inhaler (MDI) or Turbuhaler. Patients with COPD were also assigned to ELLIPTA vs Handihaler or Breezhaler. Patients demonstrated inhaler use after reading the patient information leaflet (PIL). A trained investigator assessed critical errors (i.e., those likely to result in the inhalation of significantly reduced, minimal or no medication). If the patient made errors, the investigator demonstrated the correct use of the inhaler, and the patient demonstrated inhaler use again. Fewer COPD patients made critical errors with ELLIPTA after reading the PIL vs: DISKUS, 9/171 (5%) vs 75/171 (44%); MDI, 10/80 (13%) vs 48/80 (60%); Turbuhaler, 8/100 (8%) vs 44/100 (44%); Handihaler, 17/118 (14%) vs 57/118 (48%); Breezhaler, 13/98 (13%) vs 45/98 (46%; all Po0.001). Most patients (57–70%) made no errors using ELLIPTA and did not require investigator instruction. Instruction was required for DISKUS (65%), MDI (85%), Turbuhaler (71%), Handihaler (62%) and Breezhaler (56%). Fewer asthma patients made critical errors with ELLIPTA after reading the PIL vs: DISKUS (3/70 (4%) vs 9/70 (13%), P = 0.221); MDI (2/32 (6%) vs 8/32 (25%), P = 0.074) and significantly fewer vs Turbuhaler (3/60 (5%) vs 20/60 (33%), Po0.001). More asthma and COPD patients preferred ELLIPTA over the other devices (all P ⩽0.002). Significantly, fewer COPD patients using ELLIPTA made critical errors after reading the PIL vs other inhalers. More asthma and COPD patients preferred ELLIPTA over comparator inhalers.

Gepubliceerd: NPJ Prim Care Respir Med 2017 Mar 23;27:17001
Impact factor: 2.793

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**20. Association between changes in fat distribution and biomarkers for breast cancer**

van Gemert WA, Monninkhof EM, May AM, Elias SG, van der Palen J, Veldhuis W, Stapper M, Stellato RK, Schuit JA, Peeters PH

We assessed the associations between changes in total and abdominal fat and changes in biomarkers for breast cancer risk using data of the SHAPE-2 trial. In the SHAPE-2 trial, 243 postmenopausal overweight women were included. The intervention in this trial consisted of 5-6 kg weight loss either by diet only or exercise plus diet. After 16 weeks, we measured serum sex hormones, inflammatory markers, total body fat (measured by DEXA scan) and intra and subcutaneous abdominal fat (measured by MRI). Associations between changes in different body fat depots and biomarkers were analysed by linear regression using the study cohort irrespective of randomisation to make maximal use of the distribution of changes in fat measures. We found that a loss in total body fat was associated with favourable changes in free oestradiol, free testosterone, leptin and sex hormone binding globulin (SHBG). The loss of intra-abdominal fat was associated with a decrease in free testosterone, hsCRP and leptin, and an increase in SHBG. In the multivariable analysis, the best fitted models for the biomarkers free oestradiol, SHBG leptin and adiponectin included only total body fat. For free testosterone, this was subcutaneous abdominal fat, and for hsCRP and IL-6, only intra-abdominal fat change was important. For IL-6 and adiponectin, however, associations were weak and not significant. We conclude that, in our population of healthy overweight postmenopausal women, loss of fat at different body locations was associated with changes in different types of biomarkers, known to be related to risk of breast cancer.

Gepubliceerd: Endocr Relat Cancer 2017 Jun;24(6):297-305
Impact factor: 5.267

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**21. Clinical significance of mesenteric arterial collateral circulation in patients with celiac artery compression syndrome**
van Petersen AS, Kolkman JJ, Gerrits DG, van der Palen J, Zeebregts CJ, Geelkerken RH

**Objective:** Although extensive collateral arterial circulation will prevent ischemia in most patients with stenosis of a single mesenteric artery, mesenteric ischemia may occur in these patients, for example, in patients with celiac artery compression syndrome (CACS). Variation in the extent of collateral circulation may explain the difference in clinical symptoms and variability in response to therapy; however, evidence is lacking. The objective of the study was to classify the presence of mesenteric arterial collateral circulation in patients with CACS and to evaluate the relation with clinical improvement after treatment.

**Methods:** Collateral mesenteric circulation was classified on the basis of angiographic findings. Collaterals were categorized in three groups: no visible collaterals (grade 0), collaterals seen on selective angiography only (grade 1), and collaterals visible on nonselective angiography (grade 2). Surgical release of the celiac artery in patients with suspected CACS was performed by arcuate ligament release. Clinical success after surgical revascularization was defined as an improvement in abdominal pain.
**Results:** Between 2002 and 2013, there were 135 consecutive patients with suspected CACS who were operated on. In 129 patients, preoperative angiograms allowed classification of collateral circulation. Primary assisted anatomic success was 93% (120/129). In patients with grade 0 collaterals, clinical success was 81% (39 of 48 patients); with grade 1 collaterals, 89% (25 of 28 patients); and with grade 2 collaterals, 52% (23 of 44 patients; P < .001).
**Conclusions:** Patients with CACS and with extensive collateral mesenteric arterial circulation are less likely to benefit from arcuate ligament release than are patients without this type of collateral circulation. The classification of the extent of mesenteric collateral circulation may predict and guide shared decision-making in patients with CACS.

Gepubliceerd: J Vasc Surg 2017 May;65(5):1366-74
Impact factor: 3.536

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**22. BMI predicts exercise induced bronchoconstriction in asthmatic boys**
van Veen WJ, Driessen JMM, Kersten ETG, van Leeuwen JC, Brusse-Keizer MGJ, van Aalderen WMC, Thio BJ

**Background:** Exercise induced bronchoconstriction (EIB) is a frustrating morbidity of asthma in children. Obesity has been associated with asthma and with more severe EIB in asthmatic children.
**Objectives:** To quantify the effect of BMI on the risk of the occurrence of EIB in children with asthma.
**Methods:** Data were collected from six studies in which exercise challenge tests were performed according to international guidelines. We included 212 Children aged 7-18 years, with a pediatrician-diagnosed mild-to-moderate asthma.
**Results:** A total of 103 of 212 children (49%) had a positive exercise challenge (fall of FEV1 >/= 13%). The severity of EIB, as measured by the maximum fall in FEV1 , was significantly greater in overweight and obese children compared to normal weight children (respectively 23.9% vs 17.9%; P = 0.045). Asthmatic children with a BMI z-score around +1 had a 2.9-fold higher risk of the prevalence of EIB compared to children with a BMI z-score around the mean (OR 2.9; 95%CI: 1.3-6.1; P < 0.01). An

increase in BMI z-score of 0.1 in boys led to a 1.4-fold increased risk of EIB (OR 1.4; 95%CI: 1.0-1.9; P = 0.03). A reduction in pre-exercise FEV1 was associated with a higher risk of EIB (last quartile six times higher risk compared to highest quartile (OR 6.1 [95%CI 2.5-14.5]).
**Conclusions:** The severity of EIB is significantly greater in children with overweight and obesity compared to non-overweight asthmatic children. Furthermore, this study shows that the BMI-z-score, even with a normal weight, is strongly associated with the incidence of EIB in asthmatic boys.

Gepubliceerd: Pediatr Pulmonol 2017 Sep;52(9):1130-4
Impact factor: 2.758

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**23. Substance use in individuals with mild to borderline intellectual disability: A comparison between self-report, collateral-report and biomarker analysis**
VanDerNagel JE, Kiewik M, van Dijk M, Didden R, Korzilius HP, van der Palen J, Buitelaar JK, Uges DR, Koster RA, de Jong CA

**Background:** AND AIMS: Individuals with mild or borderline intellectual disability (MBID) are at risk of substance use (SU). At present, it is unclear which strategy is the best for assessing SU in individuals with MBID. This study compares three strategies, namely self-report, collateral-report, and biomarker analysis.
**Methods and procedures:** In a sample of 112 participants with MBID from six Dutch facilities providing care to individuals with intellectual disabilities, willingness to participate, SU rates, and agreement between the three strategies were explored. The Substance use and misuse in Intellectual Disability - Questionnaire (SumID-Q; self-report) assesses lifetime use, use in the previous month, and recent use of tobacco, alcohol, cannabis, and stimulants. The Substance use and misuse in Intellectual Disability - Collateral-report questionnaire (SumID-CR; collateral-report) assesses staff members' report of participants' SU over the same reference periods as the SumID-Q. Biomarkers for SU, such as cotinine (metabolite of nicotine), ethanol, tetrahydrocannabinol (THC), and its metabolite THCCOOH, benzoylecgonine (metabolite of cocaine), and amphetamines were assessed in urine, hair, and sweat patches.
**Results:** Willingness to provide biomarker samples was significantly lower compared to willingness to complete the SumID-Q ($p<0.001$). Most participants reported smoking, drinking alcohol, and using cannabis at least once in their lives, and about a fifth had ever used stimulants. Collateralreported lifetime use was significantly lower. However, self-reported past month and recent SU rates did not differ significantly from the rates from collateral-reports or biomarkers, with the exception of lower alcohol use rates found in biomarker analysis. The agreement between self-report

and biomarker analysis was substantial (kappas 0.60-0.89), except for alcohol use (kappa 0.06). Disagreement between SumID-Q and biomarkers concerned mainly over-reporting of the SumID-Q. The agreement between SumID-CR and biomarker analysis was moderate to substantial (kappas 0.48 - 0.88), again with the exception of alcohol (kappa 0.02).
**Conclusions and implications:** In this study, the three strategies that were used to assess SU in individuals with MBID differed significantly in participation rates, but not in SU rates. Several explanations for the better-than-expected performance of self- and collateral-reports are presented. We conclude that for individuals with MBID, self-report combined with collateralreport can be used to assess current SU, and this combination may contribute to collaborative, early intervention efforts to reduce SU and its related harms in this vulnerable group.

Gepubliceerd: Res Dev Disabil 2017 Apr;63:151-9
Impact factor: 1.630

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**24. A phantom study for the comparison of different brands of computed tomography scanners and software packages for endovascular aneurysm repair sizing and planning**
Velu JF, Groot Jebbink E, de Vries JP, van der Palen JA, Slump CH, Geelkerken RH

**Objectives:** Correct sizing of endoprostheses used for the treatment of abdominal aortic aneurysms is important to prevent endoleaks and migration. Sizing requires several steps and each step introduces a possible sizing error. The goal of this study was to investigate the magnitude of these errors compared to the golden standard: a vessel phantom. This study focuses on the errors in sizing with three different brands of computed tomography angiography scanners in combination with three reconstruction software packages.
**Methods:** Three phantoms with a different diameter, altitude and azimuth were scanned with three computed tomography scanners: Toshiba Aquilion 64-slice, Philips Brilliance iCT 256-slice and Siemens Somatom Sensation 64-slice. The phantom diameters were determined in the stretched view after central lumen line reconstruction by three observers using Simbionix PROcedure Rehearsal Studio, 3mensio and TeraRecon planning software. The observers, all novices in sizing endoprostheses using planning software, measured 108 slices each. Two senior vascular surgeons set the tolerated error margin of sizing on +/-1.0 mm.
**Results:** In total, 11.3% of the measurements (73/648) were outside the set margins of +/-1.0 mm from the phantom diameter, with significant differences between the scanner types (14.8%, 12.1%, 6.9% for the Siemens scanner, Philips scanner and Toshiba scanner, respectively, p-value = 0.032), but not between the software

packages (8.3%, 11.1%, 14.4%, p-value = 0.141) or the observers (10.6%, 9.7%, 13.4%, p-value = 0.448).
**Conclusions:** It can be concluded that the errors in sizing were independent of the used software packages, but the phantoms scanned with Siemens scanner were significantly more measured incorrectly than the phantoms scanned with the Toshiba scanner. Consequently, awareness on the type of computed tomography scanner and computed tomography scanner setting is necessary, especially in complex abdominal aortic aneurysms sizing for fenestrated or branched endovascular aneurysm repair if appropriate the sizing is of upmost importance.

Gepubliceerd: Vascular 2017 Jan 1;1708538117726648
Impact factor: 0.733

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**25. Five-Year Outcome After Implantation of Zotarolimus- and Everolimus-Eluting Stents in Randomized Trial Participants and Nonenrolled Eligible Patients: A Secondary Analysis of a Randomized Clinical Trial**
von Birgelen C, van der Heijden LC, Basalus MW, Kok MM, Sen H, Louwerenburg HW, van Houwelingen KG, Stoel MG, de Man FH, Linssen GC, Tandjung K, Doggen CJ, van der Palen J, Lowik MM

**Importance:** Long-term follow-up after a clinical trial of 2 often-used, newer-generation drug-eluting stents (DESs) in a broad patient population is of interest. Comprehensive long-term outcome of eligible nonenrolled patients has never been reported.
**Objective:** To assess 5-year safety and efficacy of 2 newer-generation DESs in randomized participants with non-ST-elevation acute coronary syndromes or stable angina and to evaluate long-term outcomes of nonenrolled eligible patients treated with the same DESs.
**Design, Setting, and Participants:** The TWENTE (Real-World Endeavor Resolute vs Xience V Drug-Eluting Stent Study in Twente) trial is an investigator-initiated, patient-blinded, randomized, comparative DES trial that enrolled patients from June 18, 2008, to August 26, 2010. Most patients had non-ST-elevation acute coronary syndromes and complex lesions. Of all 1709 eligible patients, 1391 (81.4%) were treated in the TWENTE trial with zotarolimus-eluting (ZES, n = 697) or everolimus-eluting (EES, n = 694) cobalt-chromium stents. The remaining 318 eligible patients (18.6%) were not enrolled but underwent nonrandomized treatment with the same DESs. Data were analyzed from August 26, 2015, to October 11, 2016. Event rates (percentages) were derived from log-rank analysis and may differ from straightforward calculation (nominator/denominator). The 5-year follow-up of the

TWENTE participants was prespecified in the trial protocol; that of the nonenrolled participants was ad hoc.
**Main Outcomes and Measures:** Target vessel failure (TVF), a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization. Results: Of 1709 eligible participants, 1233 (72.1%) were men, 476 (27.9%) were women, and mean (SD) age was 64.6 (10.6) years. Among the 1370 of 1391 TWENTE trial participants (98.5% follow-up), TVF was similar between those in the ZES (16.1%) and EES (18.1%) groups (P = .36). Stent thrombosis rates were low: definite (7 of 697 [1.0%] vs 4 of 694 [0.6%]; P = .37) and occurred after more than 1 year in 3 (0.4%) with ZES vs 4 (0.6%) with EES (P = .69). The 318 nonenrolled eligible patients (308 patients [96.9%] of whom were followed up) were older and had more advanced disease than trial participants. Their TVF rate was higher than that of trial participants (71 of 318 [23.3%] vs 233 of 1391 [17.1%]; P = .02), which partly reflects a difference in cardiac mortality (23 of 318 [7.7%] vs 60 of 1391 [4.5%]; P = .03). Similar 5-year rates were found for myocardial infarction (91 of 1391 [6.7%] vs 22 of 318 [7.2%]; P = .80) and target vessel revascularization (129 of 1391 [9.7%] vs 34 of 318 [11.4%]; P = .36) between trial participants and nonenrolled eligible patients. In all eligible patients (ie, trial participants plus nonenrolled eligible patients), the TVF rate was only slightly higher than in trial participants only (18.3% vs 17.1%).
**Conclusions and Relevance:** Long-term outcome data from nonenrolled eligible patients support the validity of the TWENTE trial findings and present, with the trial, a strong case for the long-term safety and efficacy of the newer-generation DESs used.
**Trial Registration:** clinicaltrials.gov Identifier: NCT01066650.

Gepubliceerd: JAMA Cardiol 2017 Mar 1;2(3):268-76
Impact factor: 0

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**26. Stable State Proadrenomedullin Level in COPD Patients: A Validation Study**
Zuur-Telgen M, VanderValk P, van der Palen J, Kerstjens HA, Brusse-Keizer M

In patients with stable COPD, proadrenomedullin (MR-proADM) has been shown to be a good predictor for mortality. This study aims to provide an external validation of earlier observed cut-off values used by Zuur-Telgen et al. and Stolz.et al. in COPD patients in stable state and at hospitalization for an acute exacerbation of COPD (AECOPD). From the COMIC cohort study we included 545 COPD patients with a blood sample obtained in stable state (n = 490) and/or at hospitalization for an AECOPD (n = 101). Time to death was compared between patients with MR-proADM cut-off scores 0.71 and 0.75 nmol/L for stable state or 0.79 and 0.84 nmol/l for AECOPD. The predictive value of MR-proADM for survival was represented by the C statistic. Risk ratios were corrected for sex, age, BMI, presence of heart failure, and

GOLD stage. Patients above the cut-off of 0.75 nmol/l had a 2-fold higher risk of dying than patient below this cut-off (95% CI: 1.20-3.41). The cut-off of 0.71 nmol/l showed only a borderline significantly higher risk of 1.67 (95% CI: 0.98-2.85). The corrected odds ratios for one-year mortality were 3.15 (95% CI 1.15-8.64) and 3.70 (95% CI 1.18-11.6) in patients with MR-proADM levels above versus below the cut-off of respectively 0.75 and 0.71 nmol/l measured in stable state. MR-proADM levels in samples at hospitalization for an AECOPD were not predictive for mortality in this validation cohort. MR-proADM in stable state is a powerful predictor for mortality.

Gepubliceerd: COPD 2017 Apr;14(2):219-27
Impact factor: 2.576

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Totale impact factor: 71.284
Gemiddelde impact factor: 2.742

Aantal artikelen 1e, 2e of laatste auteur: 10
Totale impact factor: 33.440
Gemiddelde impact factor: 3.344

# Microbiologie

**1. Impact of single room design on the spread of multi-drug resistant bacteria in an intensive care unit**
Halaby T, Al Naiemi N, Beishuizen B, Verkooijen R, Ferreira JA, Klont R, Vandenbroucke-Grauls C

**Background:** Cross-transmission of nosocomial pathogens occurs frequently in intensive care units (ICU). The aim of this study was to investigate whether the introduction of a single room policy resulted in a decrease in transmission of multidrug-resistant (MDR) bacteria in an ICU.
**Methods:** We performed a retrospective study covering two periods: between January 2002 and April 2009 (old-ICU) and between May 2009 and March 2013 (new-ICU, single-room). These periods were compared with respect to the occurrence of representative MDR Gram-negative bacteria. Routine microbiological screening, was performed on all patients on admission to the ICU and then twice a week. Multi-drug resistance was defined according to a national guideline. The first isolates per patient that met the MDR-criteria, detected during the ICU admission were included in the analysis. To investigate the clonality, isolates were genotyped by DiversiLab (bioMerieux, France) or Amplified Fragment Length Polymorphism (AFLP). To guarantee the comparability of the two periods, the 'before' and 'after' periods were chosen such that they were approximately identical with respect to the following factors: number of admissions, number of beds, bed occupancy rate, per year and month.
**Results:** Despite infection prevention efforts, high prevalence of MRD bacteria continue to occur in the original facility. A marked and sustained decrease in the prevalence of MDR-GN bacteria was observed after the migration to the new ICU, while there appear to be no significant changes in the other variables including bed occupancy and numbers of patient admissions.
**Conclusion:** Single room ICU design contributes significantly to the reduction of cross transmission of MRD-bacteria**.**

Gepubliceerd: Antimicrob Resist Infect Control 2017;6:117
Impact factor: 2.989

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**2. Pseudomonas aeruginosa meningitis after visiting a swimming pool: a complicated dive**
Knapen DG, Mulder B, DeSouza F, Linssen GC, Veneman TF

Community-acquired meningitis caused by P. aeruginosa is rare and has a very high mortality rate. Early recognition and treatment is of paramount importance. We describe a case of a 75-year-old male with a P. aeruginosa meningitis which was linked to a regional swimming pool. Physicians should be aware that treatment according to the Dutch meningitis guidelines does not include coverage of infection with P. aeruginosa, which can cause, as in our case, a significant treatment delay. The case was complicated by endocarditis of an aortic valve bio-prosthesis and illustrates the incremental value of a PET-CT scan in case of high clinical and microbiological suspicion for endocarditis, while having negative echocardiographic findings.

Neth J Crit Care 2017;25(1):10-1
Impact factor: 0

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**3. Low caspofungin exposure in patients in the Intensive Care Unit**
van der Elst KC, Veringa A, Zijlstra JG, Beishuizen A, Klont R, Brummelhuis-Visser P, Uges DR, Touw DJ, Kosterink JG, van der Werf TS, Alffenaar JC

In critically ill patients, drug exposure may be influenced by altered drug distribution and clearance. Earlier studies showed that the variability in caspofungin exposure was high in Intensive Care Unit (ICU) patients. The primary objective of this study was to determine if the standard dose of caspofungin resulted in adequate exposure in critically ill patients. A multicenter prospective study in ICU patients with (suspected) invasive candidiasis was conducted in the Netherlands, from November 2013 to October 2015. Patients received standard caspofungin treatment and the exposure was determined on day 3 of treatment. An area under the concentration-time curve over 24 hours (AUC0-24h) of 98 mg*h/L was considered adequate exposure. In case of low exposure (i.e. <79 mg*h/L; >/=20% lower AUC0-24h), the caspofungin dose was increased and the exposure re-evaluated. Twenty patients were included in the study, of which 5 had a positive blood culture. The median caspofungin AUC0-24h at day 3 was 78 mg*h/L (interquartile range (IQR), 69 - 97 mg*h/L). A low AUC0-24h (<79 mg*h/L) was seen in 10 patients. The AUC0-24h was significantly and positively correlated with the caspofungin dose in mg/kg/day (P = 0.011). The median AUC0-24h with a caspofungin dose of 1 mg/kg was estimated using a pharmacokinetic model and was 114.9 mg*h/L (IQR, 103.2 - 143.5 mg*h/L). In conclusion, the caspofungin exposure in ICU patients in this study was low compared with healthy volunteers and other (non-)critically ill patients, most likely due to a larger volume of distribution. A weight-based dose regimen is probably more suitable for patients with substantially altered drug distribution.

Antimicrob Agents Chemother 2017;61(2):e01582-16
Impact factor: 4.302

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Totale impact factor: 6.600
Gemiddelde impact factor: 2.200

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 2.298
Gemiddelde impact factor: 1.149

# Neurochirurgie

**1. Predicting success of vagus nerve stimulation (VNS) from EEG symmetry**
Hilderink J, Tjepkema-Cloostermans MC, Geertsema A, Glastra-Zwiers J, de Vos CC

**Purpose:** Vagus nerve stimulation (VNS) has shown to be an effective treatment for drug resistant epilepsy, with achieving more than 50% seizure reduction in one third of the treated patients. In order to predict which patients will profit from VNS, we previously found that a low pairwise derived Brain Symmetry Index (pdBSI) could potentially predict good responders to VNS treatment. These findings however have to be validated before they can be generalized.
**Methods:** 39 patients (age 18-68 years) with medically intractable epilepsy who were referred for an implanted VNS system were included. Routine EEG registrations, recorded before implantation, were analyzed. Artefact-free epochs with eyes open and eyes closed were quantitatively analyzed. The pdBSI was tested for relation with VNS outcome one year after surgery.
**Results:** Twenty-three patients (59%) obtained a reduction in seizure frequency, of whom ten (26%) had a reduction of at least 50% (good responders) and thirteen (33%) a reduction of less than 50% (moderate responders). Sixteen patients without seizure reduction are defined as non-responders. No significant differences were found in the pdBSI of good responders (mean 0.27), moderate responders (mean 0.26) and non-responders (mean 0.25) ($p>0.05$). Besides seizure reduction, many patients (56%) reported additional positive effects of VNS in terms of seizure duration, seizure intensity and/or postictal recovery.
**Conclusion:** EEG features that correlate with VNS therapy outcome may enable better patient selection and prevent unnecessary VNS surgery. Contrary to earlier findings, this validation study suggests that pdBSI might not be helpful to predict VNS therapy outcome.

Gepubliceerd: Seizure 2017 May;48:69-73
Impact factor: 2.448

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**2. Early Electroencephalography Dynamics After Cardiac Arrest**
Hofmeijer J, Ruijter BJ, Tjepkema-Cloostermans MC, van Putten MJAM

Gepubliceerd: Crit Care Med 2017 Oct;45(10):e1093
Impact factor: 7.050

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**3. Somatosensory Evoked Potentials in Patients with Hypoxic-Ischemic Brain Injury**
Horn J, Tjepkema-Cloostermans MC

Predicting the future of patients with hypoxic-ischemic encephalopathy after successful cardiopulmonary resuscitation is often difficult. Registration of the median nerve somatosensory evoked potential (SSEP) can assist in the neurologic evaluation in these patients. In this article, the authors discuss the principles, applications, and limitations of SSEP registration in the intensive care unit, with a focus on prognostication. Registration of the SSEP is a very reliable and reproducible method, if it is performed and interpreted correctly. During SSEP recordings, great care should be taken to improve the signal-to-noise ratio. If the noise level is too high, the peripheral responses are abnormal or the response is not reproducible in a second set of stimuli; therefore, interpretation of the SSEPs cannot be done reliably. A bilaterally absent cortical SSEP response is a very reliable predictor of poor neurologic outcome in patients with HIE. It has a high specificity, but a low sensitivity, indicating that present cortical responses are a weak predictor of a good recovery. Further research is being done to increase the sensitivity. Somatosensory evoked potentials can be used in a multimodal approach for prognostication of outcome.

Gepubliceerd: Semin Neurol 2017 Feb;37(1):60-5
Impact factor: 1.891

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**4. Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands**
van Essen TA, de Ruiter GC, Kho KH, Peul WC

Several recent global traumatic brain injury (TBI) initiatives rely on practice variation in diagnostic and treatment methods to answer effectiveness questions. One of these scientific dilemmas, the surgical management of the traumatic acute subdural hematoma (ASDH) might be variable among countries, among centers within countries, and even among neurosurgeons within a center, and hence be amenable for a comparative effectiveness study. The aim of our questionnaire, therefore, was to explore variations in treatment for ASDH among neurosurgeons in similar centers in a densely populated geographical area. An online questionnaire, involving treatment decisions on six case vignettes of ASDH, was sent to 93 neurosurgeons in The Netherlands and Belgium. Clinical and radiological variables differed per case. Sixty neurosurgeons filled out the questionnaire (response rate 65%). For case vignettes with severe TBI and an ASDH, there was a modest variation in the decision to evacuate the hematoma and a large variation in the decision to combine the

evacuation with a decompressive craniectomy. The main reasons for operating were "neurological condition" and "mass effect." For ASDH and mild/moderate TBI, there was large variation in the decision of whether to operate or not, whereas "hematoma size" was the predominant motivation for surgery. Significant inter-center variation for the decision to evacuate the hematoma was observed (p = 0.01). Most pronounced was that 1 out of 7 (14%) neurosurgeons in one region chose a surgical strategy compared with 9 out of 10 (90%) in another region for the same scenario. In conclusion, variation exists in the neurosurgical management of TBI within an otherwise homogeneous setting. This variation supports the methodology of the international Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) initiative, and shaped the Dutch Neurotraumatology Quality Registry (Net-QuRe) initiative.

Gepubliceerd: J Neurotrauma 2017;34(4):881-9
Impact factor: 5.190

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**5. The Advancing Role of Neuromodulation for the Management of Chronic Treatment-Refractory Pain**
Shamji MF, De Vos C, Sharan A

Neuropathic pain is a common cause of disability and health care utilization. While judicious pharmacotherapy and management of comorbid psychological distress can provide for improved quality of life, some patients with treatment-refractory disease require more invasive therapies. Spinal cord stimulation can provide for improvement in pain and decrease in medication utilization, with level 1 evidence supporting its use across various pain etiologies including persistent postoperative neuropathic pain, complex regional pain syndrome, chronic inoperable limb ischemia, treatment refractory angina, and painful diabetic neuropathy. These procedures can be done with acceptably low morbidity and provide a cost-effective solution for those patients in whom medical therapies have failed. Technological innovation in lead design, implantable pulse generator capability, and stimulation algorithms and parameters may further enhance the success of this therapy. Neuromodulation of distal targets such as dorsal root ganglion may permit greater anatomic specificity of the therapy, whereas subthreshold stimulation with high-frequency or burst energy delivery may eliminate noxious and off-target paresthesiae. Such new technologies should be subject to rigorous evaluation as their mechanisms of action and long-term outcomes remain hitherto undefined.

Gepubliceerd: Neurosurgery 2017;80(3S):S108–S113
Impact factor: 4.889

Totale impact factor: 21.468
Gemiddelde impact factor: 4.294

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 9.228
Gemiddelde impact factor: 3.076

# Neurologie

**1. Disruption of Brain-Heart Coupling in Sepsis**
Admiraal MM, Gilmore EJ, van Putten MJAM, Zaveri HP, Hirsch LJ, Gaspard N

**Purpose:** To investigate heart rate and EEG variability and their coupling in patients with sepsis and determine their relationship to sepsis severity and severity of sepsis-associated brain dysfunction.
**Methods:** Fifty-two patients with sepsis were prospectively identified, categorized as comatose (N = 30) and noncomatose (N = 22), and compared with 11 control subjects. In a 30-minute EEG and electrocardiogram recording, heart rate variability and EEG variability (measured by the variability of relative power in a modified alpha band = RAP) and their coupled oscillations were quantified using linear (least-square periodogram and magnitude square coherence) and nonlinear (Shannon entropy and mutual information) measures. These measures were compared between the three groups and correlated with outcome, adjusting for severity of sepsis.
**Results:** Several measures of heart rate variability and EEG variability and of their coupled oscillations were significantly lower in patients with sepsis compared with controls and correlated with outcome. This correlation was not independent when adjusting for severity of sepsis.
**Conclusions:** Sepsis is associated with lower variability of both heart rate and RAP on EEG and reduction of their coupled oscillations. This uncoupling is associated with the severity of encephalopathy. Combined EEG and electrocardiogram monitoring may be used to gain insight in underlying mechanisms of sepsis and quantify brainstem or thalamic dysfunction.

Gepubliceerd: J Clin Neurophysiol 2017 May 16;34(5):413-20
Impact factor: 1.224

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**2. Transcranial magnetic stimulation as a biomarker for epilepsy**
Bauer PR, de Goede AA, Ter Braack EM, van Putten MJ, Gill RD, Sander JW

Gepubliceerd: Brain 2017 Mar 1;140(3):e18
Impact factor: 10.292

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**3. Non-Hospitalized Patients with Mild Traumatic Brain Injury: The Forgotten Minority**

de Koning ME, Scheenen ME, van der Horn HJ, Hageman G, Roks G, Spikman JM, van der Naalt J

Non-hospitalized mild traumatic brain injury (mTBI) patients comprise a substantial part of the trauma population. For these patients, guidelines recommend specialized follow-up only in the case of persistent complaints or problems in returning to previous activities. This study describes injury and outcome characteristics of non-hospitalized mTBI patients, and the possibility of predicting which of the non-hospitalized patients will return to the outpatient neurology clinic. Data from all non-hospitalized mTBI patients (Glasgow Coma Scale [GCS] score 13-15, n = 462) from a prospective follow-up study on mTBI (UPFRONT-study) conducted in three level 1 trauma centers were analyzed. At 2 weeks, and 3 and 6 months after injury, patients completed questionnaires on post-traumatic complaints, depression, anxiety, outpatient follow-up, and resumption of activities. Most patients were male (57%), with a mean age of 40 years (range 16-91 years). Injuries were most often caused by traffic accidents (32%) or falls (39%). Six months after injury, 36% showed incomplete recovery as defined by the Glasgow Outcome Scale - Extended (GOS-E). Twenty-five percent of the non-hospitalized patients returned to the outpatient neurology clinic within 6 months after injury, of which one third had not completely resumed pre-injury activities. Regression analyses showed an increased risk for outpatient follow-up for patients scoring above the cutoff value for anxiety (odds ratio [OR] = 3.0), depression (OR = 3.5), or both (OR = 3.7) 2 weeks after injury. Our findings underline that clinicians and researchers should be aware of recovery for all mTBI patients, preventing their transition into a forgotten minority.

Gepubliceerd: J Neurotrauma 2017 Jan 1;34(1):257-61
Impact factor: 5.190

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**4. Outpatient follow-up after mild traumatic brain injury: Results of the UPFRONT-study**
de Koning ME, Scheenen ME, van der Horn HJ, Hageman G, Roks G, Yilmaz T, Spikman JM, van der Naalt J

**Objective:** To investigate outpatient follow-up after mild traumatic brain injury (mTBI) by various medical specialists, for both hospitalized and non-hospitalized patients, and to study guideline adherence regarding hospital admission.
**Methods:** Patients (n = 1151) with mTBI recruited from the emergency department received questionnaires 2 weeks (n = 879), 3 months (n = 780) and 6 months (n = 668) after injury comprising outpatient follow-up by various health care providers, and outcome defined by the Glasgow Outcome Scale Extended (GOS-E) after 6 months.

**Results:** Hospitalized patients (60%) were older (46.6 +/- 19.9 vs. 40.6 +/- 18.5 years), more severely injured (GCS <15, 50% vs. 13%) with more Computed Tomography (CT) abnormalities on admission (21% vs. 2%) compared to non-hospitalized patients ($p < 0.01$) . Almost half of the patients visited a neurologist at the outpatient clinic within six months (60% of the hospitalized and 25% of the non-hospitalized patients ($chi(2) = 67.10$, $p < 0.01$)), and approximately ten per cent consulted a psychiatrist/psychologist. Outcome was unfavourable (GOS-E <7) in 34% of hospitalized and 21% of non-hospitalized patients ($chi(2) = 11.89$, $p < 0.01$).
**Conclusion:** Two-thirds of all mTBI patients consult one or more specialists within six months after injury, with 30% having an unfavourable outcome. A quarter of non-hospitalized patients was seen at the outpatient neurology clinic, underling the importance of regular follow-up of mTBI patients irrespective of hospital admittance.

Gepubliceerd: Brain Inj 2017;31(8):1102-8
Impact factor: 1.971

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**5. Prediction of work resumption and sustainability up to 1 year after mild traumatic brain injury**
de Koning ME, Scheenen ME, van der Horn HJ, Timmerman ME, Hageman G, Roks G, Spikman JM, van der Naalt J

**Objective:** To study return to work (RTW) after mild traumatic brain injury (mTBI) at several intervals after injury and to predict RTW on the basis of occupational factors in addition to demographic, personality, and injury-related factors at 6 and 12 months after injury.
**Methods:** This was a prospective cohort study (UPFRONT study, n = 1,151) of patients with mTBI admitted to the emergency department. Patients received questionnaires at 2 weeks and 3, 6, and 12 months after injury. RTW was divided into 3 levels: complete (cRTW), partial (pRTW), and no RTW.
**Results:** Rates of cRTW increased from 34% at 2 weeks to 77% at 12 months after injury, pRTW varied from 8% to 16% throughout the year. Logistic regression (complete vs incomplete RTW) demonstrated that apart from previously identified predictors such as demographics (e.g., age and education) and injury characteristics (e.g., cause and severity of injury) and indicators of psychological distress, occupational factors were of influence on work resumption after 6 months (area under the curve [AUC] = 0.82), At 12 months, however, the model was based solely on the presence of extracranial injuries and indicators of maladaptation after injury (AUC = 0.81).
**Conclusions:** RTW after mTBI is a gradual process, with varying levels of RTW throughout the first year after injury. Different predictors were relevant for short- vs

long-term work resumption, with occupational factors influencing short-term RTW. However, for both short- and long-term RTW, posttraumatic complaints and signs of psychological distress early after injury were relevant predictors, allowing early identification of patients at risk for problematic work resumption.

Gepubliceerd: Neurology 2017 Oct 31;89(18):1908-14
Impact factor: 8.320

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**6. PAIS 2 (Paracetamol [Acetaminophen] in Stroke 2): Results of a Randomized, Double-Blind Placebo-Controlled Clinical Trial**
de Ridder IR, den Hertog HM, van Gemert HM, Schreuder AH, Ruitenberg A, Maasland EL, Saxena R, van Tuijl JH, Jansen BP, Van den Berg-Vos RM, Vermeij F, Koudstaal PJ, Kappelle LJ, Algra A, van der Worp HB, Dippel DW

**Background and purpose:** Subfebrile body temperature and fever in the first days after stroke are strongly associated with unfavorable outcome. A subgroup analysis of a previous trial suggested that early treatment with paracetamol may improve functional outcome in patients with acute stroke and a body temperature of >/=36.5 degrees C. In the present trial, we aimed to confirm this finding.
**Methods:** PAIS 2 (Paracetamol [Acetaminophen] in Stroke 2) was a multicenter, randomized, double-blind, placebo-controlled clinical trial. We aimed to include 1500 patients with acute ischemic stroke or intracerebral hemorrhage within 12 hours of symptom onset. Patients were treated with paracetamol in a daily dose of 6 g or matching placebo for 3 consecutive days. The primary outcome was functional outcome at 3 months, assessed with the modified Rankin Scale and analyzed with multivariable ordinal logistic regression. Because of slow recruitment and lack of funding, the study was stopped prematurely.
**Results:** Between December 2011 and October 2015, we included 256 patients, of whom 136 (53%) were allocated to paracetamol. In this small sample, paracetamol had no effect on functional outcome (adjusted common odds ratio, 1.15; 95% confidence interval, 0.74-1.79). There was no difference in the number of serious adverse events (paracetamol n=35 [26%] versus placebo n=28 [24%]).
**Conclusions:** Treatment with high-dose paracetamol seemed to be safe. The effect of high-dose paracetamol on functional outcome remains uncertain. Therefore, a large trial of early treatment with high-dose paracetamol is still needed.
**Clinical trial registration:** URL: http://www.trialregister.nl. Unique identifier: NTR2365.

Gepubliceerd: Stroke 2017 Apr;48(4):977-82
Impact factor: 6.032

**7. The enteric nervous system and the musculature of the colon are altered in patients with spina bifida and spinal cord injury**
den Braber-Ymker M, Lammens M, van Putten MJ, Nagtegaal ID

Neurogenic bowel dysfunction occurs in a large percentage of adult patients with spina bifida (SB) and spinal cord injury (SCI), significantly affecting their quality of life. Although bowel motility is autonomously regulated by the enteric nervous system (ENS), disruption of the modulation of the ENS by extrinsic innervation as present in many patients with SB and SCI might lead to motility disorders. In order to gain insight in the pathophysiology, we studied histological changes of the neuromuscular structures in the colon of SB and SCI patients. Archival colon tissue blocks from SB (n = 13) and SCI (n = 34) patients were collected nationwide in The Netherlands and compared with control samples (n = 16). Histological (semiquantitative) evaluation of the ENS, the network of interstitial cells of Cajal (ICC), and the muscularis propria was performed using hematoxylin and eosin, periodic acid Schiff, and elastic von Gieson staining, and immunohistochemistry with antibodies against HuC/D, calretinin, S100, CD117, alpha-smooth muscle actin, and desmin. Compared to controls, SB and SCI patients showed neuronal loss and decreased nerve fiber density in the myenteric plexus. Lower nerve fiber density was significantly more often found in patients with severe bowel dysfunction. Other major findings were loss of ICCs around the myenteric plexus and fibrosis in the longitudinal muscle layer. Altered histology of the ENS may explain abnormal intestinal motility in SB and SCI patients. Furthermore, loss of myenteric nerve fibers (including enteric glial cells) may play a major role in the development of severe motility complaints.

Gepubliceerd: Virchows Arch 2017 Feb;470(2):175-84
Impact factor: 2.848

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**8. A Rate-Reduced Neuron Model for Complex Spiking Behavior**
Dijkstra K, Kuznetsov YA, van Putten MJAM, van Gils SA

We present a simple rate-reduced neuron model that captures a wide range of complex, biologically plausible, and physiologically relevant spiking behavior. This includes spike-frequency adaptation, postinhibitory rebound, phasic spiking and accommodation, first-spike latency, and inhibition-induced spiking. Furthermore, the model can mimic different neuronal filter properties. It can be used to extend existing neural field models, adding more biological realism and yielding a richer dynamical structure. The model is based on a slight variation of the Rulkov map.

Gepubliceerd: J Math Neurosci 2017 Dec 11;7(1):13
Impact factor: 0

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**9. Cross-scale effects of neural interactions during human neocortical seizure activity**
Eissa TL, Dijkstra K, Brune C, Emerson RG, van Putten MJAM, Goodman RR, McKhann GM, Jr., Schevon CA, van Drongelen W, van Gils SA

Small-scale neuronal networks may impose widespread effects on large network dynamics. To unravel this relationship, we analyzed eight multiscale recordings of spontaneous seizures from four patients with epilepsy. During seizures, multiunit spike activity organizes into a submillimeter-sized wavefront, and this activity correlates significantly with low-frequency rhythms from electrocorticographic recordings across a 10-cm-sized neocortical network. Notably, this correlation effect is specific to the ictal wavefront and is absent interictally or from action potential activity outside the wavefront territory. To examine the multiscale interactions, we created a model using a multiscale, nonlinear system and found evidence for a dual role for feedforward inhibition in seizures: while inhibition at the wavefront fails, allowing seizure propagation, feedforward inhibition of the surrounding centimeter-scale networks is activated via long-range excitatory connections. Bifurcation analysis revealed that distinct dynamical pathways for seizure termination depend on the surrounding inhibition strength. Using our model, we found that the mesoscopic, local wavefront acts as the forcing term of the ictal process, while the macroscopic, centimeter-sized network modulates the oscillatory seizure activity.

Gepubliceerd: Proc Natl Acad Sci USA 2017;114(40):10761-10766
Impact factor: 9.661

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**10. Reduced Synaptic Vesicle Recycling during Hypoxia in Cultured Cortical Neurons**
Fedorovich S, Hofmeijer J, van Putten MJ, le Feber J

Improvement of neuronal recovery in the ischemic penumbra, an area around the core of a brain infarct with some remaining perfusion, has a large potential for the development of therapy against acute ischemic stroke. However, mechanisms that lead to either recovery or secondary damage in the penumbra largely remain unclear. Recent studies in cultured networks of cortical neurons showed that failure of synaptic transmission (referred to as synaptic failure) is a critical factor in the penumbral area,

but the mechanisms that lead to synaptic failure are still under investigation. Here we used a Styryl dye, FM1-43, to quantify endocytosis and exocytosis in cultures of rat cortical neurons under normoxic and hypoxic conditions. Hypoxia in cultured cortical networks rapidly depressed endocytosis and, to a lesser extent, exocytosis. These findings support electrophysiological findings that synaptic failure occurs quickly after the induction of hypoxia, and confirms that the failing processes are at least in part presynaptic.

Gepubliceerd: Front Cell Neurosci 2017;11:32
Impact factor: 4.555

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**11. Detecting interictal discharges in first seizure patients: ambulatory EEG or EEG after sleep deprivation?**
Geut I, Weenink S, Knottnerus ILH, van Putten MJAM

**Purpose:** Uncertainty about recurrence after a first unprovoked seizure is a significant psychological burden for patients, and motivates the need for diagnostic tools with high sensitivity and specificity to assess recurrence risk. As the sensitivity of a routine EEG after a first unprovoked seizure is limited, patients often require further diagnostics. Here, we study if ambulatory EEG (aEEG) has similar diagnostic accuracy as sleep deprived EEG (sdEEG).
**Methods:** In this retrospective cohort, we included patients with an unprovoked first seizure and a normal routine EEG who subsequently underwent an sdEEG or aEEG. All EEGs were reviewed for the presence of interictal epileptiform discharges (IEDs). We calculated specificity and sensitivity of sdEEG and aEEG, using the clinical diagnosis of epilepsy as golden standard. All patients had a follow-up of one year.
**Results:** We included 104 patients. Sensitivities for sdEEG and aEEG were 45% (specificity 91%) and 63% (specificity 95%), respectively. Independent risk factor for recurrent seizure were IEDs on the additional EEG, with a relative risk of 1.5 of having a recurrent seizure within a year.
**Conclusion:** Diagnostic accuracies of sdEEG and aEEG are similar and depending on patients' and clinicians' preference both can be considered in patients with a first seizure and a normal routine EEG to determine recurrence risk.

Gepubliceerd: Seizure 2017 Aug 2;51:52-4
Impact factor: 2.448

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**12. Quantification of growth patterns of screen-detected lung cancers: The NELSON study**

Heuvelmans MA, Vliegenthart R, de Koning HJ, Groen HJM, van Putten MJAM, Yousaf-Khan U, Weenink C, Nackaerts K, de Jong PA, Oudkerk M

**Objectives:** Although exponential growth is assumed for lung cancer, this has never been quantified in vivo. Aim of this study was to evaluate and quantify growth patterns of lung cancers detected in the Dutch-Belgian low-dose computed tomography (CT) lung cancer screening trial (NELSON), in order to elucidate the development and progression of early lung cancer. MATERIALS AND
**Methods:** Solid lung nodules found at >/=3 CT examinations before lung cancer diagnosis were included. Lung cancer volume (V) growth curves were fitted with a single exponential, expressed as V=V1 exp(t/tau), with t time from baseline (days), V1 estimated baseline volume (mm3), and tau estimated time constant. The R2 coefficient of determination was used to evaluate goodness of fit. Overall volume-doubling time for the individual lung cancer is given by tau*log(2).
**Results:** Forty-seven lung cancers in 46 participants were included. Forty participants were male (87.0%); mean age was 61.7 years (standard deviation, 6.2 years). Median nodule size at baseline was 99.5mm3 (IQR: 46.8-261.8mm3). Nodules were followed for a median of 770 days (inter-quartile range: 383-1102 days) before lung cancer diagnosis. One cancer (2.1%) was diagnosed after six CT examinations, six cancers (12.8%) were diagnosed after five CTs, 14 (29.8%) after four CTs, and 26 cancers (55.3%) after three CTs. Lung cancer growth could be described by an exponential function with excellent goodness of fit (R2 0.98). Median overall volume-doubling time was 348 days (inter-quartile range: 222-492 days).
**Conclusion:** This study based on CT lung cancer screening provides in vivo evidence that growth of cancerous small-to-intermediate sized lung nodules detected at low-dose CT lung cancer screening can be described by an exponential function such as volume-doubling time.

Gepubliceerd: Lung Cancer 2017 Jun;108:48-54
Impact factor: 4.294

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**13. Predicting success of vagus nerve stimulation (VNS) from EEG symmetry**
Hilderink J, Tjepkema-Cloostermans MC, Geertsema A, Glastra-Zwiers J, de Vos CC

**Purpose:** Vagus nerve stimulation (VNS) has shown to be an effective treatment for drug resistant epilepsy, with achieving more than 50% seizure reduction in one third of the treated patients. In order to predict which patients will profit from VNS, we previously found that a low pairwise derived Brain Symmetry Index (pdBSI) could potentially predict good responders to VNS treatment. These findings however have to be validated before they can be generalized.

**Methods:** 39 patients (age 18-68 years) with medically intractable epilepsy who were referred for an implanted VNS system were included. Routine EEG registrations, recorded before implantation, were analyzed. Artefact-free epochs with eyes open and eyes closed were quantitatively analyzed. The pdBSI was tested for relation with VNS outcome one year after surgery.
**Results:** Twenty-three patients (59%) obtained a reduction in seizure frequency, of whom ten (26%) had a reduction of at least 50% (good responders) and thirteen (33%) a reduction of less than 50% (moderate responders). Sixteen patients without seizure reduction are defined as non-responders. No significant differences were found in the pdBSI of good responders (mean 0.27), moderate responders (mean 0.26) and non-responders (mean 0.25) ($p>0.05$). Besides seizure reduction, many patients (56%) reported additional positive effects of VNS in terms of seizure duration, seizure intensity and/or postictal recovery.
**Conclusion:** EEG features that correlate with VNS therapy outcome may enable better patient selection and prevent unnecessary VNS surgery. Contrary to earlier findings, this validation study suggests that pdBSI might not be helpful to predict VNS therapy outcome.

Gepubliceerd: Seizure 2017 May;48:69-73
Impact factor: 2.448

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**14. Early Electroencephalography Dynamics After Cardiac Arrest**
Hofmeijer J, Ruijter BJ, Tjepkema-Cloostermans MC, van Putten MJAM

Gepubliceerd: Crit Care Med 2017 Oct;45(10):e1093
Impact factor: 7.050

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**15. Loss and recovery of functional connectivity in cultured cortical networks exposed to hypoxia**
le Feber J, Erkamp N, van Putten MJAM, Hofmeijer J

In the core of a brain infarct, loss of neuronal function is followed by neuronal death within minutes. In an area surrounding the core (penumbra), some perfusion remains. Here, neurons initially remain structurally intact, but massive synaptic failure strongly reduces neural activity. Activity in the penumbra may eventually recover or further deteriorate toward massive cell death. Besides activity recovery, return of brain functioning requires restoration of connectivity. However, low activity has been shown to initiate compensatory mechanisms that affect network connectivity. We investigated the effect of transient hypoxia and compensatory mechanisms on activity

and functional connectivity using cultured cortical networks on multielectrode arrays. Networks were exposed to hypoxia of controlled depth (10-90% of normoxia) and duration (6-48 h). First, we determined how hypoxic depth and duration govern activity recovery. Then, we investigated connectivity changes during and after hypoxic incidents, mild enough for activity to recover. Shortly after hypoxia onset, activity and connectivity decreased. Following 4-6 h of ongoing hypoxia, we observed partial recovery. Only if the hypoxic burden was limited did connectivity show further recovery upon return to normoxia. Partial recovery during hypoxia was dominated by restored baseline connections, rather than newly formed ones. Baseline strengths of surviving (persisting or recovered) and lost connections did not differ nor did baseline activity at their "presynaptic" electrodes. However, "postsynaptic" electrodes of surviving connections were significantly more active during baseline than those of lost connections. This implies that recovery during hypoxia reflects an effective mechanism to restore network activity, which does not necessarily conserve prehypoxia connectivity.NEW & NOTEWORTHY Hypoxia reduced the firing rates of cultured neurons. Depending on hypoxic depth and duration, activity recovered during hypoxia and upon return to normoxia. Recovery (partial) during hypoxia was associated with restored baseline connections rather than newly formed ones. Predominantly, baseline connections with most active postsynaptic electrodes recovered, supporting the notion of effective activity homeostasis. This compensatory mechanism remained effective during ~20 h of hypoxia. Beyond 20 h of compensation, loss of activity and connectivity became irreversible.

Gepubliceerd: J Neurophysiol 2017 Jul 1;118(1):394-403
Impact factor: 2.396

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**16. Does prior antiplatelet treatment improve functional outcome after intra-arterial treatment for acute ischemic stroke?**
Mulder MJ, Berkhemer OA, Fransen PS, van den Berg LA, Lingsma HF, den Hertog HM, Staals J, Jenniskens SF, van Oostenbrugge RJ, van Zwam WH, Majoie CB, van der Lugt A, Dippel DW

**Background and purpose:** In patients with acute ischemic stroke who receive antiplatelet treatment, uncertainty exists about the effect and safety of intra-arterial treatment. Our aim was to study whether intra-arterial treatment in patients with prior antiplatelet treatment is safe and whether prior antiplatelet treatment modifies treatment effect.
**Methods:** All 500 MR CLEAN patients were included. We estimated the effect of intra-arterial treatment with ordinal logistic regression analysis, and tested for

interaction of antiplatelet treatment with intra-arterial treatment on outcome. Furthermore, safety parameters and serious adverse events were analyzed.
**Results:** The 144 patients (29%) on antiplatelet treatment were older, more often male, and had more vascular comorbidity. Intra-arterial treatment effect size after adjustments in antiplatelet treatment patients was 1.7 (95% confidence interval 0.9-3.2), and in no antiplatelet treatment patients 1.8 (95% confidence interval: 1.2-2.6). There was no statistically or clinically significant interaction between prior antiplatelet treatment and the relative effect of intra-arterial treatment ( p = 0.78). However, in patients on antiplatelet treatment, the effect of successful reperfusion on functional outcome in the intervention arm of the trial was doubled: the absolute risk difference for favorable outcome after successful reperfusion in patients on prior antiplatelet treatment was 39% versus 18% in patients not on prior antiplatelet treatment (Pinteraction = 0.025). Patients on antiplatelet treatment more frequently had a symptomatic intracranial hemorrhage (15%) compared to patients without antiplatelet treatment (4%), without differences between the control and intervention arm.
**Conclusions:** Prior treatment with antiplatelet agents did not modify the effect of intra-arterial treatment in patients with acute ischemic stroke presenting with an intracranial large vessel occlusion. There were no safety concerns. In patients with reperfusion, antiplatelet agents may improve functional outcome.

Gepubliceerd: Int J Stroke 2017 Jun;12(4):368-76
Impact factor: 3.314

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**17. Admission Glucose and Effect of Intra-Arterial Treatment in Patients With Acute Ischemic Stroke**
Osei E, den Hertog HM, Berkhemer OA, Fransen PSS, Roos YBWE, Beumer D, van Oostenbrugge RJ, Schonewille WJ, Boiten J, Zandbergen AAM, Koudstaal PJ, Dippel DWJ

**Background and Purpose:** Hyperglycemia on admission is common after ischemic stroke. It is associated with unfavorable outcome after treatment with intravenous thrombolysis and after intra-arterial treatment. Whether hyperglycemia influences the effect of reperfusion treatment is unknown. We assessed whether increased admission serum glucose modifies the effect of intra-arterial treatment in patients with acute ischemic stroke.
**Methods:** We used data from the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands). Hyperglycemia was defined as admission serum glucose >7.8 mmol/L. The primary outcome measure was the adjusted common odds ratio for a shift in the direction of a better outcome on the modified Rankin Scale at 90 days, estimated with ordinal

logistic regression. Secondary outcome variable was symptomatic intracranial hemorrhage. We assessed treatment effect modification of hyperglycemia and admission serum glucose levels with multiplicative interaction factors and adjusted for prognostic variables.
**Results:** Four hundred eighty-seven patients were included. Mean admission serum glucose was 7.2 mmol/L (SD, 2.2). Fifty-seven of 226 patients (25%) randomized to intra-arterial treatment were hyperglycemic compared with 61 of 261 patients (23%) in the control group. The interaction of either hyperglycemia or admission serum glucose levels and treatment effect on modified Rankin Scale scores was not significant (P=0.67 and P=0.87, respectively). The same applied for occurrence of symptomatic hemorrhage (P=0.39 for hyperglycemia, P=0.39 for admission serum glucose).
**Conclusions:** We found no evidence for effect modification of intra-arterial treatment by admission serum glucose in patients with acute ischemic stroke.
**Clinical trial registration:** URL: www.isrctn.com. Unique identifier: ISRCTN10888758.

Gepubliceerd: Stroke 2017 May;48(5):1299-305
Impact factor: 6.032

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**18. Glucose in prediabetic and diabetic range and outcome after stroke**
Osei E, Fonville S, Zandbergen AA, Koudstaal PJ, Dippel DW, den Hertog HM

**Objectives:** Newly diagnosed disturbed glucose metabolism is highly prevalent in patients with stroke. Limited data are available on their prognostic value on outcome after stroke. We aimed to assess the association of glucose in the prediabetic and diabetic range with unfavourable short-term outcome after stroke.
**Materials and methods:** We included 839 consecutive patients with ischemic stroke and 168 patients with intracerebral haemorrhage. In all nondiabetic patients, fasting glucose levels were determined on day 2-4. Prediabetic range was defined as fasting glucose of 5.6-6.9 mmol/L, diabetic range as >/=7.0 mmol/L, pre-existent diabetes as the use of anti-diabetic medication prior to admission. Outcome measures were poor functional outcome or death defined as modified Rankin Scale (mRS) score >2 and discharge not to home. The association of prediabetic range, diabetic range and pre-existent diabetes (versus normal glucose) with unfavourable outcome was expressed as odds ratios, estimated with multiple logistic regression, with adjustment for prognostic factors.
**Results:** Compared with normal glucose, prediabetic range (aOR 1.8; 95%CI 1.1-2.8), diabetic range (aOR 2.5; 95%CI 1.3-4.9) and pre-existent diabetes (aOR 2.6; 95%CI 1.6-4.0) were associated with poor functional outcome or death. Patients in

the prediabetic range (aOR 0.6; 95%CI 0.4-0.9), diabetic range (aOR 0.4; 95%CI 0.2-0.9) and pre-existent diabetes (aOR 0.6; 95%CI 0.4-0.9) were more likely not to be discharged to home.
**Conclusions:** Patients with glucose in the prediabetic and diabetic range have an increased risk of unfavourable short-term outcome after stroke. These findings illustrate the potential impact of early detection and treatment of these patients.

Gepubliceerd: Acta Neurol Scand 2017 Feb;135(2):170-5
Impact factor: 3.087

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**19. Synaptic damage underlies EEG abnormalities in postanoxic encephalopathy: A computational study**
Ruijter BJ, Hofmeijer J, Meijer HGE, van Putten MJAM

**Objective:** In postanoxic coma, EEG patterns indicate the severity of encephalopathy and typically evolve in time. We aim to improve the understanding of pathophysiological mechanisms underlying these EEG abnormalities.
**Methods:** We used a mean field model comprising excitatory and inhibitory neurons, local synaptic connections, and input from thalamic afferents. Anoxic damage is modeled as aggravated short-term synaptic depression, with gradual recovery over many hours. Additionally, excitatory neurotransmission is potentiated, scaling with the severity of anoxic encephalopathy. Simulations were compared with continuous EEG recordings of 155 comatose patients after cardiac arrest.
**Results:** The simulations agree well with six common categories of EEG rhythms in postanoxic encephalopathy, including typical transitions in time. Plausible results were only obtained if excitatory synapses were more severely affected by short-term synaptic depression than inhibitory synapses.
**Conclusions:** In postanoxic encephalopathy, the evolution of EEG patterns presumably results from gradual improvement of complete synaptic failure, where excitatory synapses are more severely affected than inhibitory synapses. The range of EEG patterns depends on the excitation-inhibition imbalance, probably resulting from long-term potentiation of excitatory neurotransmission.
**Significance:** Our study is the first to relate microscopic synaptic dynamics in anoxic brain injury to both typical EEG observations and their evolution in time.

Gepubliceerd: Clin Neurophysiol 2017 Sep;128(9):1682-95
Impact factor: 3.866

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**20. Patients "At Risk" of Suffering from Persistent Complaints after Mild Traumatic Brain Injury: The Role of Coping, Mood Disorders, and Post-Traumatic Stress**
Scheenen ME, Spikman JM, de Koning ME, van der Horn HJ, Roks G, Hageman G, van der Naalt J

Although most patients recover fully following mild traumatic brain injury (mTBI), a minority (15-25%) of all patients develop persistent post-traumatic complaints (PTC) that interfere with the resumption of previous activities. An early identification of patients who are at risk for PTC is currently performed by measuring the number of complaints in the acute phase. However, only part of this group will actually develop persisting complaints, stressing the need for studies on additional risk factors. This study aimed to compare this group of patients with many complaints with patients with few and no complaints to identify potential additional discriminating characteristics and to evaluate which of these factors have the most predictive value for being at risk. We evaluated coping style, presence of psychiatric history, injury characteristics, mood-related symptoms, and post-traumatic stress. We included 820 patients (Glasgow Coma Scale [GCS] score 13-15) admitted to three level-1 trauma centers as part of the UPFRONT-study. At 2 weeks after injury, 60% reported three or more complaints (PTC-high), 25% reported few complaints (PTC-low), and 15% reported no complaints (PTC-zero). Results showed that PTC-high consisted of more females (78% vs. 73% and 52%, $p < 0.001$), were more likely to have a psychiatric history (7% vs. 2% and 5%), and had a higher number of reported depression (22% vs. 6% and 3%, $p < 0.001$), anxiety (25% vs. 7% and 5%), and post-traumatic stress (37% vs. 27% and 19%, $p < 0.001$) than the PTC-low and PTC-zero groups. We conclude that in addition to reported complaints, psychological factors such as coping style, depression, anxiety, and post-traumatic stress symptoms had the highest predictive value and should be taken into account in the identification of at-risk patients for future treatment studies.

Gepubliceerd: J Neurotrauma 2017 Jan 1;34(1):31-7
Impact factor: 5.190

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**21. Posterior fossa progressive multifocal leukoencephalopathy: first presentation of an unknown autoimmune disease**
Scholten P, Kralt P, Jacobs B

We present a case of a 57-year-old man who presented with progressive cerebellar dysarthria and cerebellar ataxia. Additional investigations confirmed the diagnosis of progressive multifocal leukoencephalopathy (PML) in the posterior fossa. This is a

demyelinating disease of the central nervous system, caused by an opportunistic infection with John Cunningham virus. PML has previously been considered a lethal condition, but because of careful monitoring of patients with HIV and of patients using immunosuppressive drugs it is discovered in earlier stages and prognosis can be improved. Our patient had no known immune-compromising state, but further work-up revealed that the PML was most likely the first presentation of a previous untreated autoimmune disorder: sarcoidosis.

Gepubliceerd: BMJ Case Rep 2017 Oct 11;2017; 2017220990)
Impact factor: 0

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**22. Cerebral Recovery Index: Reliable Help for Prediction of Neurologic Outcome After Cardiac Arrest**
Tjepkema-Cloostermans MC, Hofmeijer J, Beishuizen A, Hom HW, Blans MJ, Bosch FH, van Putten MJAM

**Objective:** Early electroencephalography measures contribute to outcome prediction of comatose patients after cardiac arrest. We present predictive values of a new cerebral recovery index, based on a combination of quantitative electroencephalography measures, extracted every hour, and combined by the use of a random forest classifier.
**Design:** Prospective observational cohort study.
**Setting:** Medical ICU of two large teaching hospitals in the Netherlands.
**Patients:** Two hundred eighty-three consecutive comatose patients after cardiac arrest.
**Interventions:** None.
**Measurements and main results:** Continuous electroencephalography was recorded during the first 3 days. Outcome at 6 months was dichotomized as good (Cerebral Performance Category 1-2, no or moderate disability) or poor (Cerebral Performance Category 3-5, severe disability, comatose, or death). Nine quantitative electroencephalography measures were extracted. Patients were randomly divided over a training and validation set. Within the training set, a random forest classifier was fitted for each hour after cardiac arrest. Diagnostic accuracy was evaluated in the validation set. The relative contributions of resuscitation parameters and patient characteristics were evaluated. The cerebral recovery index ranges from 0 (prediction of death) to 1 (prediction of full recovery). Poor outcome could be predicted at a threshold of 0.34 without false positives at a sensitivity of 56% at 12 hours after cardiac arrest. At 24 hours, sensitivity of 65% with a false positive rate of 6% was obtained. Good neurologic outcome could be predicted with sensitivities of 63% and

58% at a false positive rate of 6% and 7% at 12 and 24 hours, respectively. Adding patient characteristics was of limited additional predictive value.
**Conclusions:** A cerebral recovery index based on a combination of intermittently extracted, optimally combined quantitative electroencephalography measures provides unequalled prognostic value for comatose patients after cardiac arrest and enables bedside EEG interpretation of unexperienced readers.

Gepubliceerd: Crit Care Med 2017 Aug;45(8):e789-e797
Impact factor: 7.050

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**23. Predicting Outcome in Postanoxic Coma: Are Ten EEG Electrodes Enough?**
Tjepkema-Cloostermans MC, Hofmeijer J, Hom HW, Bosch FH, van Putten MJAM

**Introduction:** Increasing evidence supports that early EEG recordings reliably contribute to outcome prediction in comatose patients with postanoxic encephalopathy. As postanoxic encephalopathy typically results in generalized EEG abnormalities, spatial resolution of a small number of electrodes is likely sufficient, which will reduce set-up time. Here, the authors compare a reduced and a 21-channel EEG for outcome prediction.
**Methods:** EEG recordings from 142 prospectively collected patients with postanoxic encephalopathy were reassessed by two independent reviewers using a reduced (10 electrodes) bipolar montage. Classification and prognostic accuracy were compared with the full (21 electrodes) montage. The full montage consensus was considered Gold Standard.
**Results:** Sixty-seven patients (47%) had good outcome. The agreement between the individual reviewers using the reduced montage and the Gold Standard score was good (kappa = 0.75-0.79). The interobserver agreement was not affected by reducing the number of electrodes (kappa = 0.78 for the reduced montage vs. 0.71 for the full montage). An isoelectric, low-voltage, or burst-suppression with identical bursts pattern at 24 hours invariably predicted poor outcome in both montages, with similar prognostic accuracy. A diffusely slowed or normal EEG pattern at 12 hours was associated with good outcome in both montages.
**Conclusions:** Reducing the number of electrodes from 21 to 10 does not affect EEG classification or prognostic accuracy in patients with postanoxic coma.

Gepubliceerd: J Clin Neurophysiol 2017 May;34(3):207-12
Impact factor: 1.224

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**24. Addendum to the Dutch guideline for minor head/brain injury**

van den Brand CL, van der Naalt J, Hageman G, Bienfait HP, van der Kruijk RA, Jellema K

After introduction of the Dutch guideline for 'Care for patients with minor head/brain injury' (LTH guideline) in 2010, the number of CT scans has increased. Some of these scans were for patients with only trivial trauma and may not have been necessary.- In addition, since this guideline was implemented, there have been changes in the use of anticoagulants and platelet aggregation inhibitors. Non-vitamin-K-dependent oral anticoagulants (NOACs) and platelet aggregation inhibitors, or combinations of these, are prescribed more often.- These two factors have led the Netherlands Society of Neurology to initiate a request for modification of the LTH guideline for adults in two ways: (a) identification of minimal or trivial trauma for which no CT scan is required and (b) inclusion of NOACs and platelet aggregation inhibitors, or combinations of these, in the guideline.

Gepubliceerd: Ned Tijdschr Geneeskd 2017;161(0):D2258
Impact factor: 0

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**25. Early predictors of outcome after mild traumatic brain injury (UPFRONT): an observational cohort study**
van der Naalt J, Timmerman ME, de Koning ME, van der Horn HJ, Scheenen ME, Jacobs B, Hageman G, Yilmaz T, Roks G, Spikman JM

**Background:** Mild traumatic brain injury (mTBI) accounts for most cases of TBI, and many patients show incomplete long-term functional recovery. We aimed to create a prognostic model for functional outcome by combining demographics, injury severity, and psychological factors to identify patients at risk for incomplete recovery at 6 months. In particular, we investigated additional indicators of emotional distress and coping style at 2 weeks above early predictors measured at the emergency department.
**Methods:** The UPFRONT study was an observational cohort study done at the emergency departments of three level-1 trauma centres in the Netherlands, which included patients with mTBI, defined by a Glasgow Coma Scale score of 13-15 and either post-traumatic amnesia lasting less than 24 h or loss of consciousness for less than 30 min. Emergency department predictors were measured either on admission with mTBI-comprising injury severity (GCS score, post-traumatic amnesia, and CT abnormalities), demographics (age, gender, educational level, pre-injury mental health, and previous brain injury), and physical conditions (alcohol use on the day of injury, neck pain, headache, nausea, dizziness)-or at 2 weeks, when we obtained data on mood (Hospital Anxiety and Depression Scale), emotional distress (Impact of

Event Scale), coping (Utrecht Coping List), and post-traumatic complaints. The functional outcome was recovery, assessed at 6 months after injury with the Glasgow Outcome Scale Extended (GOSE). We dichotomised recovery into complete (GOSE=8) and incomplete (GOSE</=7) recovery. We used logistic regression analyses to assess the predictive value of patient information collected at the time of admission to an emergency department (eg, demographics, injury severity) alone, and combined with predictors of outcome collected at 2 weeks after injury (eg, emotional distress and coping).
**Findings:** Between Jan 25, 2013, and Jan 6, 2015, data from 910 patients with mTBI were collected 2 weeks after injury; the final date for 6-month follow-up was July 6, 2015. Of these patients, 764 (84%) had post-traumatic complaints and 414 (45%) showed emotional distress. At 6 months after injury, outcome data were available for 671 patients; complete recovery (GOSE=8) was observed in 373 (56%) patients and incomplete recovery (GOSE </=7) in 298 (44%) patients. Logistic regression analyses identified several predictors for 6-month outcome, including education and age, with a clear surplus value of indicators of emotional distress and coping obtained at 2 weeks (area under the curve [AUC]=0.79, optimism 0.02; Nagelkerke R(2)=0.32, optimism 0.05) than only emergency department predictors at the time of admission (AUC=0.72, optimism 0.03; Nagelkerke R(2)=0.19, optimism 0.05). **Interpretation:** Psychological factors (ie, emotional distress and maladaptive coping experienced early after injury) in combination with pre-injury mental health problems, education, and age are important predictors for recovery at 6 months following mTBI. These findings provide targets for early interventions to improve outcome in a subgroup of patients at risk of incomplete recovery from mTBI, and warrant validation.
**Funding:** Dutch Brain Foundation.

Gepubliceerd: Lancet Neurol 2017 Jul;16(7):532-40
Impact factor: 26.284

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**26. Frontal alpha asymmetry as a diagnostic marker in depression: Fact or fiction? A meta-analysis**
van der Vinne N, Vollebregt MA, van Putten MJAM, Arns M

**Background:** Frontal alpha asymmetry (FAA) has frequently been reported as potential discriminator between depressed and healthy individuals, although contradicting results have been published. The aim of the current study was to provide an up to date meta-analysis on the diagnostic value of FAA in major depressive disorder (MDD) and to further investigate discrepancies in a large cross-sectional dataset.

**Methods:** SCOPUS database was searched through February 2017. Studies were included if the article reported on both MDD and controls, provided an FAA measure involving EEG electrodes F3/F4, and provided data regarding potential covariates. Hedges' d was calculated from FAA means and standard deviations (SDs). Potential covariates, such as age and gender, were explored. Post hoc analysis was performed to elucidate interindividual differences that could explain interstudy discrepancies.
**Results:** 16 studies were included (MDD: n = 1883, controls: n = 2161). After resolving significant heterogeneity by excluding studies, a non-significant Grand Mean effect size (ES) was obtained (d = - 0.007;CI = [- 0.090]-[0.075]). Crosssectional analyses showed a significant three-way interaction for Gender x Age x Depression severity in the depressed group, which was prospectively replicated in an independent sample.
**Conclusions:** The main result was a non-significant, negligible ES, demonstrating limited diagnostic value of FAA in MDD. The high degree of heterogeneity across studies indicates covariate influence, as was confirmed by crosssectional analyses, suggesting future studies should address this Gender x Age x Depression severity interaction. Upcoming studies should focus more on prognostic and research domain usages of FAA rather than a pure diagnostic tool.

Gepubliceerd: Neuroimage Clin 2017;16:79-87
Impact factor: 4.348

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**27. Risk factors and outcomes associated with post-traumatic headache after mild traumatic brain injury**
Yilmaz T, Roks G, de Koning M, Scheenen M, van der Horn H, Plas G, Hageman G, Schoonman G, Spikman J, van der Naalt J

**Objectives:** To determine the prevalence and potential risk factors of acute and chronic post-traumatic headache (PTH) in patients with mild to moderate traumatic brain injury (TBI) in a prospective longitudinal observational multicentre study. Acute PTH (aPTH) is defined by new or worsening of pre-existing headache occurring within 7 days after trauma, whereas chronic PTH (cPTH) is defined as persisting aPTH >3 months after trauma. An additional goal was to study the impact of aPTH and cPTH in terms of return to work (RTW), anxiety and depression.
**Methods:** This was a prospective observational study conducted between January 2013 and February 2014 in three trauma centres in the Netherlands. Patients aged 16 years and older with a GCS score of 9-15 on admission to the ED, with loss of consciousness and/or amnesia were prospectively enrolled. Follow-up questionnaires were completed at 2 weeks and 3 months after injury with the Head Injury Symptom Checklist, the Hospital Anxiety and Depression Scale and RTW scale.

**Results:** In total, 628 patients were enrolled in the study, 469 completed the 2-week questionnaire (75%) at 2 weeks and 409 (65%) at 3 months. At 2 weeks, 238 (51%) had developed aPTH and at 3 months 95 (23%) had developed cPTH. Female gender, younger age, headache immediately at the ED and CT scan abnormalities increased the risk for aPTH. Risk factors for cPTH were female gender and headache at the ED. Patients with cPTH were less likely to have returned to work than those without cPTH (35% vs 14%, P=0.001). Patients with aPTH and cPTH more often report anxiety (20% and 28%, P=0.001) and depression (19% and 28%, P=0.001) after trauma in comparison with the group without PTH (10% anxiety and 8% depression).
**Conclusions:** PTH is an important health problem with a significant impact on long-term outcome of TBI patients. Several risk factors were identified, which can aid in early identification of subjects at risk for PTH.

Gepubliceerd: Emerg Med J 2017 Dec;34(12):800-5
Impact factor: 1.861

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**28. Clopidogrel or ticagrelor in acute coronary syndrome patients treated with newer-generation drug-eluting stents: CHANGE DAPT**
Zocca P, van der Heijden LC, Kok MM, Lowik MM, Hartmann M, Stoel MG, Louwerenburg JW, de Man FHAF, Linssen GCM, Knottnerus IL, Doggen CJM, van Houwelingen KG, von Birgelen C

**Aims:** Acute coronary syndrome (ACS) guidelines have been changed, favouring more potent antiplatelet drugs. We aimed to evaluate the safety and efficacy of a ticagrelor- instead of a clopidogrel-based primary dual antiplatelet (DAPT) regimen in ACS patients treated with newer-generation drug-eluting stents (DES).
**Methods and Results:** CHANGE DAPT (clinicaltrials.gov: NCT03197298) assessed 2,062 consecutive real-world ACS patients, treated by percutaneous coronary intervention (PCI), the primary composite endpoint being net adverse clinical and cerebral events (NACCE: all-cause death, any myocardial infarction, stroke or major bleeding). In the clopidogrel (CP; December 2012-April 2014) and ticagrelor periods (TP; May 2014-August 2015), 1,009 and 1,053 patients were treated, respectively. TP patients were somewhat older, underwent fewer transfemoral procedures, and received fewer glycoprotein IIb/IIIa inhibitors. In the TP, the one-year NACCE rate was higher (5.1% vs. 7.8%; HR 1.53 [95% CI: 1.08-2.17]; p=0.02). Assessment of non-inferiority (pre-specified margin: 2.7%) was inconclusive (risk difference: 2.64 [95% CI: 0.52-4.77]; pnon-inferiority=0.48). TP patients had more major bleeding (1.2% vs. 2.7%; p=0.02) while there was no benefit in ischaemic endpoints. Propensity score-adjusted multivariate analysis confirmed higher NACCE (adj. HR

1.75 [95% CI: 1.20-2.55]; p=0.003) and major bleeding risks during TP (adj. HR 2.75 [95% CI: 1.34-5.61]; p=0.01).
**Conclusions:** In this observational study, the guideline-recommended ticagrelor-based primary DAPT regimen was associated with an increased event risk in consecutive ACS patients treated with newer-generation DES.

Gepubliceerd: EuroIntervention 2017 Nov 20;13(10):1168-76
Impact factor: 5.193

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Totale impact factor: 136.178
Gemiddelde impact factor: 4.864

Aantal artikelen 1e, 2e of laatste auteur: 10
Totale impact factor: 39.237
Gemiddelde impact factor: 3.924

# Orthopedie

**1. The effectiveness of the use of a digital activity coaching system in addition to a two-week home-based exercise program in patients after total knee arthroplasty: study protocol for a randomized controlled trial**
Harmelink KEM, Zeegers AVCM, Tonis TM, Hullegie W, Nijhuis-van der Sanden MWG, Staal JB

**Background:** There is consistent evidence that supervised programs are not superior to home-based programs after total knee arthroplasty (TKA), especially in patients without complications. Home-based exercise programs are effective, but we hypothesize that their effectiveness can be improved by increasing the adherence to physical therapy advice to reach an adequate exercise level during the program and thereafter. Our hypothesis is that an activity coaching system (accelerometer-based activity sensor), alongside a home-based exercise program, will increase adherence to exercises and the activity level, thereby improving physical functioning and recovery. The objective of this study is to determine the effectiveness of an activity coaching system in addition to a home-based exercise program after a TKA compared to only the home-based exercise program with physical functioning as outcome.
**Methods:** This study is a single-blind randomized controlled trial. Both the intervention (n = 55) and the control group (n = 55) receive a two-week home-based exercise program, and the intervention group receives an additional activity coaching system. This is a hand-held electronic device together with an app on a smartphone providing information and advice on exercise behavior during the day. The primary outcome is physical functioning, measured with the Timed Up and Go test (TUG) after two weeks, six weeks and three months. Secondary outcomes are 1) adherence to the activity level (activity diary); 2) physical functioning, measured with the 2-Minute Walk Test (2MWT) and the Knee Osteoarthritis Outcome Score; 3) quality of life (SF-36); 4) healthcare use up to one year postoperatively and 5) cost-effectiveness. Data are collected preoperatively, three days, two and six weeks, three months and one year postoperatively.
**Discussion:** The strengths of the study are the use of both performance-based tests and self-reported questionnaires and the personalized tailored program after TKA given by specialized physical therapists. Its weakness is the lack of blinding of the participants to treatment allocation. Outcomes are generalizable to uncomplicated patients as defined in the inclusion criteria.
**Trial registration:** The trial is registered in the Dutch Trial Register (www.trialregister.nl, NTR 5109) (March 22, 2015).

Gepubliceerd: BMC Musculoskelet Disord 2017 Jul 5;18(1):290

Impact factor: 1.739

**2. Effectiveness of rehabilitation after a total hip arthroplasty: a protocol for an observational study for the comparison of usual care in the Netherlands versus Germany**
Seeber GH, Wijnen A, Lazovic D, Bulstra SK, Dietz G, van Lingen CP, Stevens M

**Introduction:** Osteoarthritis is the most common joint disorder worldwide. Total hip arthroplasty (THA) is considered one of the most effective treatments for end-stage hip osteoarthritis. The number of THAs is expected to increase dramatically in the coming decades. Usual postoperative rehabilitation after primary THA differs between the German and the Dutch system. In the Netherlands, patients undergo fast-track surgery and are discharged into their home environment within a few days without receiving any aftercare. In Germany, patients stay in the hospital for about 12 days before being transferred to a rehabilitation centre for a period of 3 weeks. The superficially more cost-effective Dutch system of usual care after THA is judged critically in both countries due to suboptimal rehabilitation outcomes. The aim of this study is therefore to compare the Dutch with the German usual care rehabilitation after primary THA. It is hypothesised that the German procedure is more effective in terms of functional outcomes and patient satisfaction than the Dutch procedure and that in the long run the German approach is more cost-effective than the Dutch system.
**Methods and analysis:** Medical effectiveness will be assessed at four different time points by means of patient self-reported questionnaires and functional tests. Assessments include the Hip disability and Osteoarthritis Outcome Score, Patient Acceptable Symptom State, Short Form 36, EuroQol 5 Dimensions 3 Level Questionnaire, Timed Up & Go Test and Five Times Sit-to-Stand Test. Additionally, long-term economic aspects in both countries will be assessed from a societal perspective, to get a first impression on whether cutting costs for rehabilitation, as practised in the Netherlands, really disburdens the healthcare system efficiently.
**Ethics and dissemination:** The study is approved by the Institutional Review Boards of both University Medical Center Groningen (METc2015/483) and Hannover Medical School (no 2874-2015) and will be conducted according to the principles of the Declaration of Helsinki (64th, 2013). The results of the study will be published in international peer-reviewed scientific journals. Patient data will be presented anonymously in any publication or scientific journal.
**Trial registration number:** DRKS00011345.

Gepubliceerd: BMJ Open 2017 Aug 11;7(8):e016020
Impact factor: 2.369

**3. Sequelae of large-head metal-on-metal hip arthroplasties: Current status and future prospects**
van Lingen CP, Zagra LM, Ettema HB, Verheyen CC

Large-head metal-on-metal (MoM) bearings were re-popularised in the late 1990s with the introduction of modern hip resurfacing (HR), followed closely by large metal head total hip arthroplasty (THA). A worldwide increase in the use of MoM hip arthroplasty subsequently saw a sharp decline, due to serious complications.MoM was rapidly adopted in the early 2000s until medical device alerts were issued by government regulatory agencies and national and international organisations, leading to post-marketing surveillance and discontinuation of these implants.Guidelines for MoM hip implant follow-up differ considerably between regulatory authorities worldwide; this can in part be attributed to missing or conflicting evidence.The authors consider that the use of large-head MoM THA should be discontinued. MoM HR should be approached with caution and, when considered, should be used only in patients who meet all of the recommended selection criteria, which limits its indications considerably.The phased introduction of new prostheses should be mandatory in future. Close monitoring of outcomes and long-term follow-up is also necessary for the introduction of new prostheses. Cite this article: van Lingen CP, Zagra LM, Ettema HB, Verheyen CC. Sequelae of large-head metal-on-metal hip arthroplasties: current status and future prospects.

Gepubliceerd: EFORT Open Rev 2016 Oct;1(10):345-53
Impact factor: 0

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**4. Anterior cruciate ligament- and hamstring tendon-derived cells: in vitro differential properties of cells involved in ACL reconstruction**
Ghebes CA, Kelder C, Schot T, Renard AJ, Pakvis DF, Fernandes H, Saris DB

Anterior cruciate ligament (ACL) reconstruction involves the replacement of the torn ligament with a new graft, often a hamstring tendon (HT). Described as similar, the ACL and HT have intrinsic differences related to their distinct anatomical locations. From a cellular perspective, identifying these differences represents a step forward in the search for new cues that enhance recovery after the reconstruction. The purpose of this study was to characterize the phenotype and multilineage potential of ACL- and HT-derived cells. ACL- and HT-derived cells were isolated from tissue harvest from patients undergoing total knee arthroplasty (TKA) or ACL reconstruction. In total, three ACL and three HT donors were investigated. Cell morphology, self-renewal

potential (CFU-F), surface marker profiling, expression of tendon/ligament-related markers (PCR) and multilineage potential were analysed for both cell types; both had fibroblast-like morphology and low self-renewal potential. No differences in the expression of tendon/ligament-related genes or a selected set of surface markers were observed between the two cell types. However, differences in their multilineage potential were observed: while ACL-derived cells showed a high potential to differentiate into chondrocytes and adipocytes, but not osteoblasts, HT-derived cells showed poor potential to form adipocytes, chondrocytes and osteoblasts. Our results demonstrated that HT-derived cells have low multilineage potential compared to ACL-derived cells, further highlighting the need for extrinsic signals to fully restore the function of the ACL upon reconstruction. 

Gepubliceerd in: J Tissue Eng Regen Med 2017 Apr;11(4):1077-88
Impact factor: 4.710

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Totale impact factor: 8.818
Gemiddelde impact factor: 2.205

Aantal artikelen 1e, 2e of laatste auteur: 2
Totale impact factor: 1.739
Gemiddelde impact factor: 0.870

# Pathologie

**1. Integrin alpha 11 in the regulation of the myofibroblast phenotype: implications for fibrotic diseases**
Bansal R, Nakagawa S, Yazdani S, van Baarlen J, Venkatesh A, Koh AP, Song WM, Goossens N, Watanabe H, Beasley MB, Powell CA, Storm G, Kaminski N, van Goor H, Friedman SL, Hoshida Y, Prakash J

Tissue fibrosis, characterized by excessive accumulation of aberrant extracellular matrix (ECM) produced by myofibroblasts, is a growing cause of mortality worldwide. Understanding the factors that induce myofibroblastic differentiation is paramount to prevent or reverse the fibrogenic process. Integrin-mediated interaction between the ECM and cytoskeleton promotes myofibroblast differentiation. In the present study, we explored the significance of integrin alpha 11 (ITGA11), the integrin alpha subunit that selectively binds to type I collagen during tissue fibrosis in the liver, lungs and kidneys. We showed that ITGA11 was co-localized with alpha-smooth muscle actin-positive myofibroblasts and was correlatively induced with increasing fibrogenesis in mouse models and human fibrotic organs. Furthermore, transcriptome and protein expression analysis revealed that ITGA11 knockdown in hepatic stellate cells (liver-specific myofibroblasts) markedly reduced transforming growth factor beta-induced differentiation and fibrotic parameters. Moreover, ITGA11 knockdown dramatically altered the myofibroblast phenotype, as indicated by the loss of protrusions, attenuated adhesion and migration, and impaired contractility of collagen I matrices. Furthermore, we demonstrated that ITGA11 was regulated by the hedgehog signaling pathway, and inhibition of the hedgehog pathway reduced ITGA11 expression and fibrotic parameters in human hepatic stellate cells in vitro, in liver fibrosis mouse model in vivo and in human liver slices ex vivo. Therefore, we speculated that ITGA11 might be involved in fibrogenic signaling and might act downstream of the hedgehog signaling pathway. These findings highlight the significance of the ITGA11 receptor as a highly promising therapeutic target in organ fibrosis.

Gepubliceerd: Exp Mol Med 2017 Nov 17;49(11):e396
Impact factor: 5.063

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**2. Tumor-stroma ratio as prognostic factor for survival in rectal adenocarcinoma: A retrospective cohort study**
Scheer R, Baidoshvili A, Zoidze S, Elferink MAG, Berkel AEM, Klaase JM, van Diest PJ

**Aim:** To evaluate the prognostic value of the tumor-stroma ratio (TSR) in rectal cancer.
**Methods:** TSR was determined on hematoxylin and eosin stained histological sections of 154 patients treated for rectal adenocarcinoma without prior neoadjuvant treatment in the period 1996-2006 by two observers to assess reproducibility. Patients were categorized into three categories: TSR-high [carcinoma percentage (CP) >/= 70%], TSR-intermediate (CP 40%, 50% and 60%) and TSR-low (CP </= 30%). The relation between categorized TSR and survival was analyzed using Cox proportional hazards model.
**Results:** Thirty-six (23.4%) patients were scored as TSR-low, 70 (45.4%) as TSR-intermediate and 48 (31.2%) as TSR-high. TSR had a good interobserver agreement (kappa = 0.724, concordance 82.5%). Overall survival (OS) and disease free survival (DFS) were significantly better for patients with a high TSR (P = 0.01 and P = 0.02, respectively). A similar association existed for disease specific survival (P = 0.06). In multivariate analysis, patients without lymph node metastasis and an intermediate TSR had a higher risk of dying from rectal cancer (HR = 5.27, 95%CI: 1.54-18.10), compared to lymph node metastasis negative patients with a high TSR. This group also had a worse DFS (HR = 6.41, 95%CI: 1.84-22.28). An identical association was seen for OS. These relations were not seen in lymph node metastasis positive patients.
**Conclusion:** The TSR has potential as a prognostic factor for survival in surgically treated rectal cancer patients, especially in lymph node negative cases.

Gepubliceerd: World J Gastrointest Oncol 2017 Dec 15;9(12):466-74
Impact factor: 0

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**3. Pleuroparenchymal fibroelastosis with prominent thrombosis**
van der Oord K, Rietema H, von der Thusen JH, Thunnissen E

Gepubliceerd: Pathol Int 2017 Jan;67(1):56-8
Impact factor: 1.465

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**4. Breast Cancer Survival of BRCA1/BRCA2 Mutation Carriers in a Hospital-Based Cohort of Young Women**
Schmidt MK, van den Broek AJ, Tollenaar RA, Smit VT, Westenend PJ, Brinkhuis M, Oosterhuis WJ, Wesseling J, Janssen-Heijnen ML, Jobsen JJ, Jager A, Voogd AC, van Leeuwen FE, van 't Veer LJ

**Background:** The primary aim of the study was to investigate prognosis and long-term survival in young breast cancer patients with a BRCA1 or BRCA2 germline mutation compared with noncarriers. The secondary aim was to investigate whether differences in survival originate from associations with tumor characteristics, second cancers, and/or treatment response.
**Methods:** We established a cohort of invasive breast cancer patients diagnosed younger than age 50 years in 10 Dutch hospitals between 1970 and 2003. BRCA1/2 testing of most prevalent mutations was mainly done using DNA isolate from formalin-fixed paraffin-embedded nontumor tissue. Survival estimates were derived using Cox regression and competing risk models.
**Results:** In 6478 breast cancer patients, we identified 3.2% BRCA1 and 1.2% BRCA2 mutation carriers. BRCA1 mutation carriers had a worse overall survival independent of clinico-pathological/treatment characteristics, compared with noncarriers (adjusted hazard ratio [HR] = 1.20, 95% confidence interval [CI] = 0.97 to 1.47), though only statistically significant in the first five years of follow-up (adjusted HR = 1.40, 95% CI = 1.07 to 1.84). A large part of the worse survival was explained by incidence of ovarian cancers. Breast cancer-specific, disease-free, and metastasis-free survival results were less pronounced and mostly statistically nonsignificant but in the same direction with those of overall survival. Overall survival was worse, although not statistically significantly, within the ER-negative or ER-positive, grade 3, and small tumor subgroups. The worse survival was most pronounced in non-chemotherapy-treated patients (adjusted HR = 1.54, 95% CI = 1.08 to 2.19). Power for BRCA2 mutation carriers was limited; only after five years' follow-up overall survival was worse (adjusted HR = 1.47, 95% CI = 1.00 to 2.17).
**Conclusions:** BRCA1/2 mutation carriers diagnosed with breast cancer before age 50 years are prone to a worse survival, which is partly explained by differences in tumor characteristics, treatment response, and second ovarian cancers.

Gepubliceerd: J Natl Cancer Inst 2017 Aug 1;109(8)
Impact factor: 13.757

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**5. Short telomere length in IPF lung associates with fibrotic lesions and predicts survival**
Snetselaar R, van Batenburg AA, van Oosterhout MFM, Kazemier KM, Roothaan SM, Peeters T, van der Vis JJ, Goldschmeding R, Grutters JC, van Moorsel CHM

Telomere maintenance dysfunction has been implicated in the pathogenesis of Idiopathic Pulmonary Fibrosis (IPF). However, the mechanism of how telomere length is related to fibrosis in the lungs is unknown. Surgical lung biopsies of IPF patients typically show a heterogeneous pattern of non-fibrotic and fibrotic areas. Therefore,

telomere length (TL) in both lung areas of patients with IPF and familial interstitial pneumonia was compared, specifically in alveolar type 2 (AT2) cells. Fluorescent in situ hybridization was used to determine TL in non-fibrotic and fibrotic areas of 35 subjects. Monochrome multiplex quantitative polymerase chain reaction (MMqPCR) was used for 51 whole lung biopsies and blood TL measurements. For sporadic IPF subjects, AT2 cell TL in non-fibrotic areas was 56% longer than in fibrotic areas. No such difference was observed in the surrounding lung cells. In subjects carrying a telomerase reverse transcriptase (TERT) mutation, AT2 cell TL was significantly shorter than in sporadic subjects. However, no difference in surrounding cell TL was observed between these subject groups. Finally, using biopsy MMqPCR TL measurements, it was determined that IPF subjects with shortest lung TL had a significantly worse survival than patients with long TL. This study shows that shortening of telomeres critically affects AT2 cells in fibrotic areas, implying TL as a cause of fibrogenesis. Furthermore, short lung telomere length is associated with decreased survival.

Gepubliceerd: PLoS One 2017;12(12):e0189467
Impact factor: 2.806

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**6. Soft tissue angiofibroma: Clinicopathologic, immunohistochemical and molecular analysis of 14 cases**

Bekers EM, Groenen PJTA, Verdijk MAJ, Raaijmakers-van Geloof WL, Roepman P, Vink R, Gilhuijs NDB, van Gorp JM, Bovee JVMG, Creytens DH, Flanagan AM, Suurmeijer AJH, Mentzel T, Arbajian E, Flucke U

Soft tissue angiofibroma is rare and has characteristic histomorphological and genetic features. For diagnostic purposes, there are no specific antibodies available. Fourteen lesions (6 females, 8 males; age range 7-67 years) of the lower extremities (12) and trunk (2) were investigated by immunohistochemistry, including for the first time NCOA2. NCOA2 was also tested in a control group of other spindle cell lesions. The known fusion-genes (AHRR-NCOA2 and GTF2I-NCOA2) were examined using RT-PCR in order to evaluate their diagnostic value. Cases in which no fusion gene was detected were additionally analysed by RNA sequencing. All cases tested showed nuclear expression of NCOA2. However, this was not specific since other spindle cell neoplasms also expressed this marker in a high percentage of cases. Other variably positive markers were EMA, SMA, desmin and CD34. STAT6 was negative in the cases tested. By RT-PCR for the most frequently observed fusions, an AHRR-NCOA2 fusion transcript was found in 9/14 cases. GTF2I-NCOA2 was not detected in the remaining cases (n = 3). RNA sequencing revealed three additional positive cases; two harbored a AHRR-NCOA2 fusion and one case a novel GAB1-

ABL1 fusion. Two cases failed molecular analysis due to poor RNA quality. In conclusion, the AHRR-NCOA2 fusion is a frequent finding in soft tissue angiofibroma, while GTF2I-NCOA2 seems to be a rare genetic event. For the first time, we report a GAB1-ABL1 fusion in a soft tissue angiofibroma of a child. Nuclear expression of NCOA2 is not discriminating when compared with other spindle cell neoplasms.

Gepubliceerd: Genes Chromosomes Cancer 2017 Oct;56(10):750-7
Impact factor: 3.696

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**7. Accuracy of the online prognostication tools PREDICT and Adjuvant! for early-stage breast cancer patients younger than 50 years**

Engelhardt EG, van den Broek AJ, Linn SC, Wishart GC, Rutgers EJT, van de Velde AO, Smit VTHB, Voogd AC, Siesling S, Brinkhuis M, Seynaeve C, Westenend PJ, Stiggelbout AM, Tollenaar RAEM, van Leeuwen FE, van 't Veer LJ, Ravdin PM, Pharaoh PDP, Schmidt MK

**Importance:** Online prognostication tools such as PREDICT and Adjuvant! are increasingly used in clinical practice by oncologists to inform patients and guide treatment decisions about adjuvant systemic therapy. However, their validity for young breast cancer patients is debated.
**Objective:** To assess first, the prognostic accuracy of PREDICT's and Adjuvant! 10-year all-cause mortality, and second, its breast cancer-specific mortality estimates, in a large cohort of breast cancer patients diagnosed <50 years.
**Design:** Hospital-based cohort.
**Setting:** General and cancer hospitals.
**Participants:** A consecutive series of 2710 patients without a prior history of cancer, diagnosed between 1990 and 2000 with unilateral stage I-III breast cancer aged <50 years.
**Main outcome measures:** Calibration and discriminatory accuracy, measured with C-statistics, of estimated 10-year all-cause and breast cancer-specific mortality.
**Results:** Overall, PREDICT's calibration for all-cause mortality was good (predicted versus observed) meandifference: -1.1% (95%CI: -3.2%-0.9%; P = 0.28). PREDICT tended to underestimate all-cause mortality in good prognosis subgroups (range meandifference: -2.9% to -4.8%), overestimated all-cause mortality in poor prognosis subgroups (range meandifference: 2.6%-9.4%) and underestimated survival in patients < 35 by -6.6%. Overall, PREDICT overestimated breast cancer-specific mortality by 3.2% (95%CI: 0.8%-5.6%; P = 0.007); and also overestimated it seemingly indiscriminately in numerous subgroups (range meandifference: 3.2%-14.1%). Calibration was poor in the cohort of patients with the lowest and those with the highest mortality probabilities. Discriminatory accuracy was moderate-to-good for

all-cause mortality in PREDICT (0.71 [95%CI: 0.68 to 0.73]), and the results were similar for breast cancer-specific mortality. Adjuvant!'s calibration and discriminatory accuracy for both all-cause and breast cancer-specific mortality were in line with PREDICT's findings.
**Conclusions:** Although imprecise at the extremes, PREDICT's estimates of 10-year all-cause mortality seem reasonably sound for breast cancer patients <50 years; Adjuvant! findings were similar. Prognostication tools should be used with caution due to the intrinsic variability of their estimates, and because the threshold to discuss adjuvant systemic treatment is low. Thus, seemingly insignificant mortality overestimations or underestimations of a few percentages can significantly impact treatment decision-making.

Gepubliceerd: Eur J Cancer 2017 Jun;78:37-44
Impact factor: 6.029

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**8. Potential Targets' Analysis Reveals Dual PI3K/mTOR Pathway Inhibition as a Promising Therapeutic Strategy for Uterine Leiomyosarcomas-an ENITEC Group Initiative**
Cuppens T, Annibali D, Coosemans A, Trovik J, Ter HN, Colas E, Garcia-Jimenez A, van d, V, Kruitwagen RP, Brinkhuis M, Zikan M, Dundr P, Huvila J, Carpen O, Haybaeck J, Moinfar F, Salvesen HB, Stukan M, Mestdagh C, Zweemer RP, Massuger LF, Mallmann MR, Wardelmann E, Mints M, Verbist G, Thomas D, Gomme E, Hermans E, Moerman P, Bosse T, Amant F

**Purpose:** Uterine sarcomas are rare and heterogeneous tumors characterized by an aggressive clinical behavior. Their high rates of recurrence and mortality point to the urgent need for novel targeted therapies and alternative treatment strategies. However, no molecular prognostic or predictive biomarkers are available so far to guide choice and modality of treatment.
**Experimental Design:** We investigated the expression of several druggable targets (phospho-S6(S240) ribosomal protein, PTEN, PDGFR-alpha, ERBB2, and EGFR) in a large cohort of human uterine sarcoma samples (288), including leiomyosarcomas, low-grade and high-grade endometrial stromal sarcomas, undifferentiated uterine sarcomas, and adenosarcomas, together with 15 smooth muscle tumors of uncertain malignant potential (STUMP), 52 benign uterine stromal tumors, and 41 normal uterine tissues. The potential therapeutic value of the most promising target, p-S6(S240), was tested in patient-derived xenograft (PDX) leiomyosarcoma models.
**Results:** In uterine sarcomas and STUMPs, S6(S240) phosphorylation (reflecting mTOR pathway activation) was associated with higher grade (P = 0.001) and recurrence (P = 0.019), as shown by logistic regression. In addition, p-S6(S240)

correlated with shorter progression-free survival (P = 0.034). Treatment with a dual PI3K/mTOR inhibitor significantly reduced tumor growth in 4 of 5 leiomyosarcoma PDX models (with tumor shrinkage in 2 models). Remarkably, the 4 responding models showed basal p-S6(S240) expression, whereas the nonresponding model was scored as negative, suggesting a role for p-S6(S240) in response prediction to PI3K/mTOR inhibition.
**Conclusions:** Dual PI3K/mTOR inhibition represents an effective therapeutic strategy in uterine leiomyosarcoma, and p-S6(S240) expression is a potential predictive biomarker for response to treatment. Clin Cancer Res; 23(5); 1274-85. (c)2017 AACR.

Gepubliceerd: Clin Cancer Res 2017 Mar 1;23(5):1274-85
Impact factor: 9.619

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**9. BRAF Mutations in Pulmonary Langerhans Cell Histiocytosis: A Multicentre Survey**
den Bakker MA, Gathier GHGK, Thunnissen E, Vreuls W, 't Hart N, ten Berge RL, Seldenrijk K, van Suylen RJ, van Nistelrooij AMJ, van Nederveen FH, Bendek M, Timens W, Breeuwsma N, Brinkhuis M, Sietsma H, Stavast J, von der Thusen JH, Dinjens WNM, Dubbink HJ

Pulmonary Langerhans cell histiocytosis (PLCH) is a smokingrelated condition in which aggregates of Langerhans cells admixed with other inflammatory cells are found in lung tissue. The general view is that PLCH is a reactive condition rather than a neoplasm. However, in small series BRAF c.1799T>A (p.V600E) mutations have been identified which raise the possibility that PLCH may have features of a neoplasm after all. Because the reported cases are few in number, we undertook a multi-institute survey of BRAF mutations in adult smokers. We found BRAF V600E mutations in 57% of our cohort of 61 patients. No significant relation with age or gender and BRAF status was found. Our series confirms the presence of BRAF V600E mutations in a large proportion of PLCH patients.

Gepubliceerd: J Pulm Med 2017;1(1):1-4
Impact factor: 0

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Totale impact factor: 42.435
Gemiddelde impact factor: 4.715

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

Totale impact factor: 1.465
Gemiddelde impact factor: 0.733

# Plastische Chirurgie

**1. The new opt-out Dutch National Breast Implant Registry - Lessons learnt from the road to implementation**
Rakhorst HA, Mureau MAM, Cooter RD, McNeil J, van Hooff M, van der Hulst R, Hommes J, Hoornweg M, Moojen-Zaal L, Liem P, Mathijssen IMJ

An estimated 1-3% of all women in the Netherlands carry breast implants. Since the introduction five decades ago, problems with a variety of breast implants have emerged with direct consequences for the patients' health. Plastic surgeons worldwide reacted through campaigning for auditing on long-term implant quality, surgeon performance, and institutional outcomes in implant registries. Especially, the PIP implant scandal of 2010 demonstrated the paucity of epidemiological data and uncovered a weakness in our ability to even 'track and trace' patients. In addition, a recent report of the Dutch Institute of National Health showed a lack of compliance of 100% of breast implant producers to CE requirements. These arguments stress the need for an independent implant registry. Insufficient capture rates or dependence from the implant producers made the variety of national and international patient registries unreliable. The Dutch Breast Implant Registry (DBIR) is unique because it is an opt-out registry without the need for informed consent and thus a high capture rate. Furthermore, an estimated 95% of breast implants are implanted by board-certified plastic surgeons. Funding was received from a non-governmental organisation to increase the quality of health care in the Netherlands, and maintenance is gathered by 25 euros per implant inserted. This article describes the way the Dutch have set up their system, with special attention to the well-known hurdles of starting a patient registry. Examples include: funding, medical ethical issues, opt out system, benchmarking, quality assurance as well as governance and collaboration. The Dutch consider their experience and data shareware for others to be used globally to the benefit of patient safety and quality improvement.

Gepubliceerd in: J Plast Reconstr Aesthet Surg 2017 Oct;70(10):1354-60
Impact factor: 2.048

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**2. Differences in the Reporting of Racial and Socioeconomic Disparities among Three Large National Databases for Breast Reconstruction**
Kamali P, Zettervall SL, Wu W, Ibrahim AM, Medin C, Rakhorst HA, Schermerhorn ML, Lee BT, Lin SJ

**Background:** Research derived from large-volume databases plays an increasing role in the development of clinical guidelines and health policy. In breast cancer research, the Surveillance, Epidemiology and End Results, National Surgical Quality Improvement Program, and Nationwide Inpatient Sample databases are widely used. This study aims to compare the trends in immediate breast reconstruction and identify the drawbacks and benefits of each database.
**Methods:** Patients with invasive breast cancer and ductal carcinoma in situ were identified from each database (2005-2012). Trends of immediate breast reconstruction over time were evaluated. Patient demographics and comorbidities were compared. Subgroup analysis of immediate breast reconstruction use per race was conducted.
**Results:** Within the three databases, 1.2 million patients were studied. Immediate breast reconstruction in invasive breast cancer patients increased significantly over time in all databases. A similar significant upward trend was seen in ductal carcinoma in situ patients. Significant differences in immediate breast reconstruction rates were seen among races; and the disparity differed among the three databases. Rates of comorbidities were similar among the three databases.
**Conclusions:** There has been a significant increase in immediate breast reconstruction; however, the extent of the reporting of overall immediate breast reconstruction rates and of racial disparities differs significantly among databases. The Nationwide Inpatient Sample and the National Surgical Quality Improvement Program report similar findings, with the Surveillance, Epidemiology and End Results database reporting results significantly lower in several categories. These findings suggest that use of the Surveillance, Epidemiology and End Results database may not be universally generalizable to the entire U.S. POPULATION:.

Gepubliceerd in: Plast Reconstr Surg 2017 Apr;139(4):795-807
Impact factor: 3.784

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**3. Trends in immediate breast reconstruction and early complication rates among older women: A big data analysis**
Kamali P, Curiel D, van Veldhuisen CL, Bucknor AEM, Lee BT, Rakhorst HA, Lin SJ

**Background:** Although approximately 57% of breast cancer (BC) diagnoses are in older patients (>60 years), only 4.1-14% receives breast reconstruction (BR). This has been attributed to physician concerns about operative complications. This paper aims to: 1) analyze the 30-day complication rates in the older patient population undergoing immediate breast reconstruction (IBR); and 2) analyze links between complication type and category of reconstruction.

**Methods:** Using the ACS-NSQIP database (2005-2014), all women older than 60 years of age diagnosed with BC and DCIS were identified. IBR and complication rates were plotted for all ages. Patients were divided into those with and those without complications. Patient demographics and co-morbidities were compared. Complications within each type of reconstruction were analyzed.
**Results:** Of the 4450 BC and 1104 DCIS patients, 22.3% (BC) and 20.9% (DCIS) had complications. IBR decreased significantly with increased age ($P < 0.00$ in both cohorts), while complication rates remained stable across all ages ($P = 0.32$ in BC, $P = 0.69$ in DCIS patients). Patients were well matched in terms of demographics.
**Conclusions:** The rates of breast reconstruction decrease with increasing age. Despite increasing age, associated complication rates in IBR patients remained stable.

Gepubliceerd in: J Surg Oncol 2017 Jun;115(7):870-7
Impact factor: 2.993

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**4. Prevalence of psychiatric comorbidities among women undergoing free tissue autologous breast reconstruction**
Becherer BE, Kamali P, Paul MA, Wu W, Curiel DA, Rakhorst HA, Lee B, Lin SJ, Kansal KJ

**Background and objectives:** Autologous breast reconstruction (BR) can be a stressful life event. Therefore, women undergoing mastectomy and autologous BR are required to have sufficient coping mechanisms. Although mental health problems are widespread, information regarding the prevalence of psychiatric diagnosis among these patients is scarce.
**Methods:** Retrospective analysis was performed using data from a large tertiary teaching hospital and the Nationwide Inpatient Sample (NIS) database. Patients undergoing autologous BR after mastectomy were included and evaluated for psychiatric disorders. Prevalence of each disorder, timing of diagnosis (preoperative or postoperative), and data per age group were reviewed.
**Results:** Between 2004 and 2014, 817 patients were included from the institutional database and 26 399 from the NIS database. Preoperatively, 15.3% of the patients were diagnosed with a psychiatric disorder within our institution and 17.6% nationwide ($P < 0.001$). Postoperatively, 20.5% of the institutional patients were diagnosed with a psychiatric disorder. No major differences in prevalence were seen between age groups.
**Conclusions:** Approximately, one in six patients were diagnosed with a psychiatric comorbidity preoperatively. Postoperatively, an additional 20.5% developed a

psychiatric disorder. There was no difference in prevalence and timing of diagnosis between age groups.

Gepubliceerd in: J Surg Oncol 2017 Dec;116(7):803-10
Impact factor: 2.993

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Totale impact factor: 11.698
Gemiddelde impact factor: 2.925

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 2.048
Gemiddelde impact factor: 2.048

# Radiologie

**1. Long-Term Results of Endovascular Treatment of Atherosclerotic Stenoses or Occlusions of the Coeliac and Superior Mesenteric Artery in Patients With Mesenteric Ischaemia**
Bulut T, Oosterhof-Berktas R, Geelkerken RH, Brusse-Keizer M, Stassen EJ, Kolkman JJ

**Introduction:** Over the past decade, primary percutaneous mesenteric artery stenting (PMAS) has become an alternative to open revascularisation for treatment of mesenteric ischaemia. Institutes have presented favourable short-term outcomes after PMAS, but there is a lack of data on long-term stent patency.
**Methods:** One hundred and forty-one patients treated by PMAS for acute and chronic mesenteric ischaemia over an 8 year period were studied. Anatomical success was assessed by duplex ultrasound and/or CT angiography. A stenosis >/=70% was considered to be a failure.
**Results:** Eighty-six coeliac arteries (CA) and 99 superior mesenteric arteries (SMA) were treated with PMAS in 141 patients. Nine CAs (10%) and 30 SMAs (30%) were occluded at the time of treatment. Median follow-up was 32 months (IQR 20-46). The overall primary patency rate at 12 and 60 months was 77.0% and 45.0%. The overall primary assisted patency rate was 90.3% and 69.8%. Overall secondary patency was 98.3% and 93.6%.
**Conclusion:** This study shows excellent long-term secondary patencies after PMAS, comparable with published data on long-term patencies after open surgical revascularisation.

Gepubliceerd: Eur J Vasc Endovasc Surg 2017 Feb 18;53(4):583-90
Impact factor: 4.061

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**2. Chronic Mesenteric Ischemia: when and how to intervene on patients with celiac/SMA stenosis**
Blauw J, Bulut T, Eenhoorn P, Beuk RJ, Brusse-Keizer M, Kolkman J, Geelkerken RH

Studies that compared open surgical mesenteric artery repair (OSMAR) with percutaneous mesenteric artery stenting (PMAS) in patients with chronic mesenteric ischemia (CMI) are based on merely older studies in which only a minority of patients received PMAS. This does not reflect the current PMAS-first choice treatment paradigm. This article focused on the present opinions and changes in outcomes of OSMAR for CMI in the era of preferred use of PMAS. Patients who received OSMAR

for CMI from 1997 until 2014 in a tertiary referral centre for chronic mesenteric ischemia were included in this report. Patients were divided into two groups, the historical OSMAR preferred group and present PMAS preferred group. Patient characteristics, SVS comorbidity severity score, clinical presentation and number of diseased mesenteric arteries were not significantly changed after the widespread introduction of PMAS. In the present PMAS first era there were trends of less open surgical mesenteric artery multi-vessel repair, less antegrade situated bypasses, decreased clinical success but improved survival after OSMAR. Elective OSMAR should only be used in patients with substantial physiologic reserve and who have unfavourable mesenteric lesions, failed PMAS or multiple recurrences of in-stent stenosis/occlusion. PMAS in CMI patients is evolved from 'bridge to surgery' to nowadays first choice treatment and "bridge to repeated PMAS" in almost all patients with CMI.

Gepubliceerd: J Cardiovasc Surg (Torino) 2017;58(2):321-8
Impact factor: 1.632

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**3. Mesenteric vascular treatment 2016: from open surgical repair to endovascular revascularization**
Blauw JT, Bulut T, Oderich GS, Geelkerken BR

The rise of endovascular techniques has improved the outcome of mesenteric ischemia. Key principle in reduction of morbidity and mortality is "revascularization first, resection later". We believe that mesenteric ischemia is a clinical challenge demanding 24/7 multidisciplinary team availability. This article describes the current insights into treatment of mesenteric ischemia.

Gepubliceerd: Best Pract Res Clin Gastroenterol 2017 Feb;31(1):75-84
Impact factor: 3.762

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**4. Clinical significance of mesenteric arterial collateral circulation in patients with celiac artery compression syndrome**
van Petersen AS, Kolkman JJ, Gerrits DG, van der Palen J, Zeebregts CJ, Geelkerken RH

**Objective:** Although extensive collateral arterial circulation will prevent ischemia in most patients with stenosis of a single mesenteric artery, mesenteric ischemia may occur in these patients, for example, in patients with celiac artery compression syndrome (CACS). Variation in the extent of collateral circulation may explain the

difference in clinical symptoms and variability in response to therapy; however, evidence is lacking. The objective of the study was to classify the presence of mesenteric arterial collateral circulation in patients with CACS and to evaluate the relation with clinical improvement after treatment.
**Methods:** Collateral mesenteric circulation was classified on the basis of angiographic findings. Collaterals were categorized in three groups: no visible collaterals (grade 0), collaterals seen on selective angiography only (grade 1), and collaterals visible on nonselective angiography (grade 2). Surgical release of the celiac artery in patients with suspected CACS was performed by arcuate ligament release. Clinical success after surgical revascularization was defined as an improvement in abdominal pain.
**Results:** Between 2002 and 2013, there were 135 consecutive patients with suspected CACS who were operated on. In 129 patients, preoperative angiograms allowed classification of collateral circulation. Primary assisted anatomic success was 93% (120/129). In patients with grade 0 collaterals, clinical success was 81% (39 of 48 patients); with grade 1 collaterals, 89% (25 of 28 patients); and with grade 2 collaterals, 52% (23 of 44 patients; P < .001).
**Conclusions:** Patients with CACS and with extensive collateral mesenteric arterial circulation are less likely to benefit from arcuate ligament release than are patients without this type of collateral circulation. The classification of the extent of mesenteric collateral circulation may predict and guide shared decision-making in patients with CACS.

Gepubliceerd: J Vasc Surg 2017 May;65(5):1366-74
Impact factor: 3.536

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Totale impact factor: 12.991
Gemiddelde impact factor: 3.248

Aantal artikelen 1e, 2e of laatste auteur: 3
Totale impact factor: 9.455
Gemiddelde impact factor: 3.152

# Radiotherapie

**1. Timed Get Up and Go Test and Geriatric 8 Scores and the Association With (Chemo-)Radiation Therapy Noncompliance and Acute Toxicity in Elderly Cancer Patients**

Middelburg JG, Mast ME, de Kroon M, Jobsen JJ, Rozema T, Maas H, Baartman EA, Geijsen D, van der Leest AH, van den Bongard DJ, van Loon J, Budiharto T, Coebergh JW, Aarts MJ, Struikmans H

**Purpose:** To investigate whether the Geriatric 8 (G8) and the Timed Get Up and Go Test (TGUGT) and clinical and demographic patient characteristics were associated with acute toxicity of radiation therapy and noncompliance in elderly cancer patients being irradiated with curative intent.
**Methods and materials:** Patients were eligible if aged >/=65 years and diagnosed with breast, non-small cell lung, prostate, head and neck, rectal, or esophageal cancer, and were referred for curative radiation therapy. We recorded acute toxicity and noncompliance and identified potential predictors, including the G8 and TGUGT.
**Results:** We investigated 402 patients with a median age of 72 years (range, 65-96 years). According to the G8, 44.4% of the patients were frail. Toxicity grade >/=3 was observed in 22% of patients who were frail according to the G8 and 9.1% of patients who were not frail. The difference was 13% (confidence interval 5.2%-20%; P=.0006). According to the TGUGT 18.8% of the patients were frail; 21% of the frail according to the TGUGT developed toxicity grade >/=3, compared with 13% who were not frail. The difference was 7.3% (confidence interval -2.7% to 17%; P=.11). Overall compliance was 95%. Toxicity was most strongly associated with type of primary tumor, chemotherapy, age, and World Health Organization performance status. Compliance was associated with type of primary tumor and age.
**Conclusions:** The usefulness of the TGUGT and G8 score in daily practice seems to be limited. Type of primary tumor, chemoradiotherapy, age, and World Health Organization performance status were more strongly associated with acute toxicity. Only chemoradiotherapy and age were associated with noncompliance. Overall the compliance was very high. To allow better-informed treatment decisions, a more accurate prediction of toxicity is desirable

Gepubliceerd: Int J Radiat Oncol Biol Phys 2017 Jul 15;98(4):843-9
Impact factor: 5.133

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**2. Breast Cancer Survival of BRCA1/BRCA2 Mutation Carriers in a Hospital-Based Cohort of Young Women**

Schmidt MK, van den Broek AJ, Tollenaar RA, Smit VT, Westenend PJ, Brinkhuis M, Oosterhuis WJ, Wesseling J, Janssen-Heijnen ML, Jobsen JJ, Jager A, Voogd AC, van Leeuwen FE, van 't Veer LJ

**Background:** The primary aim of the study was to investigate prognosis and long-term survival in young breast cancer patients with a BRCA1 or BRCA2 germline mutation compared with noncarriers. The secondary aim was to investigate whether differences in survival originate from associations with tumor characteristics, second cancers, and/or treatment response.
**Methods:** We established a cohort of invasive breast cancer patients diagnosed younger than age 50 years in 10 Dutch hospitals between 1970 and 2003. BRCA1/2 testing of most prevalent mutations was mainly done using DNA isolate from formalin-fixed paraffin-embedded nontumor tissue. Survival estimates were derived using Cox regression and competing risk models.
**Results:** In 6478 breast cancer patients, we identified 3.2% BRCA1 and 1.2% BRCA2 mutation carriers. BRCA1 mutation carriers had a worse overall survival independent of clinico-pathological/treatment characteristics, compared with noncarriers (adjusted hazard ratio [HR] = 1.20, 95% confidence interval [CI] = 0.97 to 1.47), though only statistically significant in the first five years of follow-up (adjusted HR = 1.40, 95% CI = 1.07 to 1.84). A large part of the worse survival was explained by incidence of ovarian cancers. Breast cancer-specific, disease-free, and metastasis-free survival results were less pronounced and mostly statistically nonsignificant but in the same direction with those of overall survival. Overall survival was worse, although not statistically significantly, within the ER-negative or ER-positive, grade 3, and small tumor subgroups. The worse survival was most pronounced in non-chemotherapy-treated patients (adjusted HR = 1.54, 95% CI = 1.08 to 2.19). Power for BRCA2 mutation carriers was limited; only after five years' follow-up overall survival was worse (adjusted HR = 1.47, 95% CI = 1.00 to 2.17).
**Conclusions:** BRCA1/2 mutation carriers diagnosed with breast cancer before age 50 years are prone to a worse survival, which is partly explained by differences in tumor characteristics, treatment response, and second ovarian cancers

Gepubliceerd: J Natl Cancer Inst 2017 Aug 1;109(8)
Impact factor: 13.757

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**3. The influence of timing of radiation therapy following breast-conserving surgery on 10-year disease-free survival**
van Maaren MC, Bretveld RW, Jobsen JJ, Veenstra RK, Groothuis-Oudshoorn CG, Struikmans H, Maduro JH, Strobbe LJ, Poortmans PM, Siesling S

**Background:** The Dutch guidelines advise to start radiation therapy (RT) within 5 weeks following breast-conserving surgery (BCS). However, much controversy exists regarding timing of RT. This study investigated its effect on 10-year disease-free survival (DFS) in a Dutch population-based cohort.
**Methods:** All women diagnosed with primary invasive stage I-IIIA breast cancer in 2003 treated with BCS+RT were included. Two populations were studied. Population 1 excluded patients receiving chemotherapy before RT. Analyses were stratified for use of adjuvant systemic therapy (AST). Population 2 included patients treated with chemotherapy, and compared chemotherapy before (BCS-chemotherapy-RT) and after RT (BCS-RT-chemotherapy). DFS was estimated using multivariable Cox regression. Locoregional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS) and overall survival (OS) were secondary outcomes.
**Results:** Population 1 (n=2759) showed better DFS and DMFS for a time interval of >55 than a time interval of <42 days. Patients treated with AST showed higher DFS for >55 days (hazards ratio (HR) 0.60 (95% confidence interval (CI): 0.38-0.94)) and 42-55 days (HR 0.64 (95% CI: 0.45-0.91)) than <42 days. Results were similar for DMFS, while timing did not affect LRRFS and OS. For patients without AST, timing was not associated with DFS, DMFS and LLRFS, but 10-year OS was significantly lower for 42-55 and >55 days compared to <42 days. In population 2 (n=1120), timing did not affect survival in BCS-chemotherapy-RT. In BCS-RT-chemotherapy, DMFS was higher for >55 than <42 days.
**Conclusions:** Starting RT shortly after BCS seems not to be associated with a better long-term outcome. The common position that RT should start as soon as possible following surgery in order to increase treatment efficacy can be questioned

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Impact factor: 6.176

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**4. Feedback preferences of patients, professionals and health insurers in integrated head and neck cancer care**
van Overveld LFJ, Takes RP, Vijn TW, Braspenning JCC, de Boer JP, Brouns JJA, Bun RJ, van Dijk BAC, Dortmans JAWF, Dronkers EAC, van Es RJJ, Hoebers FJP, Kropveld A, Langendijk JA, Langeveld TPM, Oosting SF, Verschuur HP, de Visscher JGAM, van Weert S, Merkx MAW, Smeele LE, Hermens RPMG

**Background:** Audit and feedback on professional practice and health care outcomes are the most often used interventions to change behaviour of professionals and improve quality of health care. However, limited information is available regarding preferred feedback for patients, professionals and health insurers.

**Objective:** Investigate the (differences in) preferences of receiving feedback between stakeholders, using the Dutch Head and Neck Audit as an example.
**Methods:** A total of 37 patients, medical specialists, allied health professionals and health insurers were interviewed using semi-structured interviews. Questions focussed on: "Why," "On what aspects" and "How" do you prefer to receive feedback on professional practice and health care outcomes?
**Results:** All stakeholders mentioned that feedback can improve health care by creating awareness, enabling self-reflection and reflection on peers or colleagues, and by benchmarking to others. Patients prefer feedback on the actual professional practice that matches the health care received, whereas medical specialists and health insurers are interested mainly in health care outcomes. All stakeholders largely prefer a bar graph. Patients prefer a pie chart for patient-reported outcomes and experiences, while Kaplan-Meier survival curves are preferred by medical specialists. Feedback should be simple with firstly an overview, and 1-4 times a year sent by e-mail. Finally, patients and health professionals are cautious with regard to transparency of audit data.
**Conclusions:** This exploratory study shows how feedback preferences differ between stakeholders. Therefore, tailored reports are recommended. Using this information, effects of audit and feedback can be improved by adapting the feedback format and contents to the preferences of stakeholders

Gepubliceerd: Health Expect 2017 Jun 15;20(6):1275-88
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Totale impact factor: 26.735
Gemiddelde impact factor: 6.684

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 1.669
Gemiddelde impact factor: 1.669

# Reumatologie

**1. A mixed-methods process evaluation of a goal management intervention for patients with polyarthritis**
Arends RY, Bode C, Taal E, van de Laar MA

Process evaluations of newly developed interventions are necessary to identify effective and less effective intervention components. First aim of this study was to identify key components of a psychosocial goal management intervention from the perspective of participants, and second aim was to evaluate the intervention's fidelity. A mixed-methods approach was applied to 24 interviews with participants post-intervention and 16 audio recordings of random training sessions. Participants experienced three key components: (1) the content, in which specific exercises helped to raise awareness and (intention to) change goal management behaviour, (2) person-focused approach, specifically, the nurse as trainer and personal fit of the approach, and (3) social mechanisms, including facilitating group processes and interpersonal processes. Adherence to the protocol by the trainers was high, while differences were found in the degree to which they were able to apply the intended collaborative approach and psychological communication skills. The applied design provided valuable insights into the processes that took place. Both the effects experienced by participants in relationship to the content, approach and social mechanisms as well as the strengths and weaknesses found with regard to fidelity provide insights that can inform the development and implementation of person-focused interventions

Gepubliceerd: Psychol Health 2017 Jan;32(1):38-60
Impact factor: 2.450

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**2. The added value of synovial fluid centrifugation for monosodium urate and calcium pyrophosphate crystal detection**
Boumans D, Hettema ME, Vonkeman HE, Maatman RG, van de Laar MA

The aim of the study was to assess the added value of synovial fluid (SF) centrifugation for microscopic monosodium urate (MSU) and calcium pyrophosphate (CPP) crystal detection in patients with arthritis. This is a prospective observational study using SF samples from joints of patients undergoing joint arthrocentesis. Two blinded observers assessed the SF smears by polarized light microscopy for the presence of crystals before as well as after centrifugation. SF samples were collected from 98 patients with arthritis. After exclusion, 87 samples were eligible for inclusion.

Of each sample, 2 smears before and after centrifugation were prepared and microscopically examined, resulting in 348 smears per observer. Observer 1 identified MSU crystals in 18.4% and CPP in 9.2% of the smears before as well as after centrifugation. No extra MSU crystal-positive smears were identified after centrifugation. However, centrifugation yielded 4 additional CPP crystal-positive smears. Observer 2 identified MSU crystals in 15.5% and CPP crystals in 6.3% of the smears before as well as after centrifugation. Centrifugation yielded 2 additional MSU crystal-positive smears and 4 CPP crystal-positive smears. Monosodium urate crystals were well recognized without centrifugation. Centrifugation of SF had limited additional value for increasing the amount of MSU-positive smears. However, CPP crystals were identified in a higher number of smears after centrifugation than before. Therefore, centrifugation may be of additional value in selected patients with suspected calcium pyrophosphate deposition disease and to a lesser extent for gout

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Impact factor: 2.365

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**3. Quality of care in gout: a clinical audit on treating to the target with urate lowering therapy in real-world gout patients**
Janssen CA, Jansen TLTA, Oude Voshaar MAH, Vonkeman HE, van de Laar MAFJ

The current paper aimed to describe the quality of care for gout patients by showing the clinical outcomes achieved in two patient cohorts in which differing targeted urate lowering therapy (ULT) treatment approaches were employed, both aiming to reach the European League Against Rheumatism recommended serum urate (sUA) targets. A retrospective medical chart review study was conducted. Data from the medical records of gout patients from two clinical centers in The Netherlands, both applying targeted ULT treatments (albeit using different approaches), were reviewed. Patients in cohort A were given a combination of xanthine oxidase inhibitors with uricosurics if treatment with allopurinol monotherapy failed to reach sUA target levels, whereas patients in cohort B were treated with sequential monotherapy. Data on patient characteristics and clinical outcomes were collected. A total of 177 patient dossiers were included: 99 from cohort A and 78 from cohort B. The great majority (n = 146, 82.5%) of the patients in both cohorts had a current sUA level <360 micromol/L. In addition, more than half (n = 104, 58.8%) of the patients met the stringent sUA target level of <300 micromol/L. The largest reductions in mean sUA levels were observed for patients who were treated with combination therapy. This clinical audit of two cohorts of gout patients provides initial-yet promising-results regarding the proportion of real-world gout patients in whom recommended that sUA target levels can be

achieved, and demonstrates the added value that a targeted treatment approach may have in reaching these goals

Gepubliceerd: Rheumatol Int 2017 Jul 26;37(9):1435-40
Impact factor: 1.824

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**4. Development of a web-based patient decision aid for initiating disease modifying anti-rheumatic drugs using user-centred design methods**
Nota I, Drossaert CHC, Melissant HC, Taal E, Vonkeman HE, Haagsma CJ, van de Laar MAFJ

**Background:** A main element of patient-centred care, Patient Decision Aids (PtDAs) facilitate shared decision-making (SDM). A recent update of the International Patient Decision Aids Standards (IPDAS) emphasised patient involvement during PtDA development, but omitted a methodology for doing so. This article reports on the value of user-centred design (UCD) methods for the development of a PtDA that aims to support inflammatory arthritis patients in their choice between disease modifying anti-rheumatic drugs (DMARDs).
**Methods:** The IPDAS development process model in combination with UCD methods were applied. The process was overseen by an eight-member multidisciplinary steering group. Patients and health professionals were iteratively consulted. Qualitative in-depth interviews combined with rapid prototyping were conducted with patients to assess their needs for specific functionality, content and design of the PtDA. Group meetings with health professionals were organized to assess patients' needs and to determine how the PtDA should be integrated into patient pathways. The current literature was reviewed to determine the clinical evidence to include in the PtDA. To evaluate usability among patients, they were observed using the PtDA while thinking aloud and then interviewed.
**Results:** The combination of patient interviews with rapid prototyping revealed that patients wanted to compare multiple DMARDs both for their clinical aspects and implications for daily life. Health professionals mainly wanted to refer patients to a reliable, easily adjustable source of information about DMARDs. A web-based PtDA was constructed consisting of four parts: 1) general information about SDM, inflammatory arthritis and DMARDs; 2) an application to compare particular DMARDs; 3) value clarification exercises; and 4) a printed summary of patients' notes, preferences, worries and questions that they could bring to discuss with their rheumatologist.
**Conclusions:** The study demonstrated that UCD methods can be of great value for the development of PtDAs. The early, iterative involvement of patients and health professionals was helpful in developing a novel user-friendly PtDA that allowed

patients to choose between DMARDs. The PtDA fits the values of all stakeholders and easily integrates with the patient pathway and daily workflow of health professionals. This collaborative designed PtDA may improve SDM and patient participation in arthritis care

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Impact factor: 1.643

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**5. Measuring Disease Exacerbation and Flares in Rheumatoid Arthritis: Comparison of Commonly Used Disease Activity Indices and Individual Measures**

Oude Voshaar MAH, Ghiti Moghadam M, Vonkeman HE, Ten Klooster PM, van Schaardenburg D, Tekstra J, Visser H, van de Laar MAFJ, Jansen TL

**Objective:** To evaluate and compare the utility of commonly used outcome measures for assessing disease exacerbation or flare in patients with rheumatoid arthritis (RA).
**Methods:** Data from the Dutch Potential Optimalisation of (Expediency) and Effectiveness of Tumor necrosis factor-alpha blockers (POET) study, in which 462 patients discontinued their tumor necrosis factor-alpha inhibitor, were used. The ability of different measures to discriminate between those with and without physician-reported flare or medication escalation at the 3-month visit (T2) was evaluated by calculating effect size (ES) statistics. Responsiveness to increased disease activity was compared between measures by standardizing change scores (SCS) from baseline to the 3-month visit. Finally, the incremental validity of individual outcome measures beyond the Simplified Disease Activity Score was evaluated using logistic regression analysis.
**Results:** The SCS were greater for disease activity indices than for any of the individual measures. The 28-joint Disease Activity Score, Clinical Disease Activity Index, and Simplified Disease Activity Index performed similarly. Pain and physician's (PGA) and patient's global assessment (PtGA) of disease activity were the most responsive individual measures. Similar results were obtained for discriminative ability, with greatest ES for disease activity indices followed by pain, PGA, and PtGA. Pain was the only measure to demonstrate incremental validity beyond SDAI in predicting 3-month flare status.
**Conclusion:** These results support the use of composite disease activity indices, patient-reported pain and disease activity, and physician-reported disease activity for measuring disease exacerbation or identifying flares of RA. Physical function, acute-phase response, and the auxiliary measures fatigue, participation, and emotional well-being performed poorly

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Impact factor: 3.150

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**6. Measuring everyday functional competence using the Rasch assessment of everyday activity limitations (REAL) item bank**
Oude Voshaar MAH, Ten Klooster PM, Vonkeman HE, van de Laar MAFJ

**Objective:** Traditional patient-reported physical function instruments often poorly differentiate patients with mild-to-moderate disability. We describe the development and psychometric evaluation of a generic item bank for measuring everyday activity limitations in outpatient populations.
**Study design and setting:** Seventy-two items generated from patient interviews and mapped to the International Classification of Functioning, Disability and Health (ICF) domestic life chapter were administered to 1128 adults representative of the Dutch population. The partial credit model was fitted to the item responses and evaluated with respect to its assumptions, model fit, and differential item functioning (DIF). Measurement performance of a computerized adaptive testing (CAT) algorithm was compared with the SF-36 physical functioning scale (PF-10).
**Results:** A final bank of 41 items was developed. All items demonstrated acceptable fit to the partial credit model and measurement invariance across age, sex, and educational level. Five- and ten-item CAT simulations were shown to have high measurement precision, which exceeded that of SF-36 physical functioning scale across the physical function continuum. Floor effects were absent for a 10-item empirical CAT simulation, and ceiling effects were low (13.5%) compared with SF-36 physical functioning (38.1%). CAT also discriminated better than SF-36 physical functioning between age groups, number of chronic conditions, and respondents with or without rheumatic conditions.
**Conclusion:** The Rasch assessment of everyday activity limitations (REAL) item bank will hopefully prove a useful instrument for assessing everyday activity limitations. T-scores obtained using derived measures can be used to benchmark physical function outcomes against the general Dutch adult population

Gepubliceerd: Qual Life Res 2017 Jun 21;26(11):2949-59
Impact factor: 2.344

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**7. Rheumatoid arthritis-specific cardiovascular risk scores are not superior to general risk scores: a validation analysis of patients from seven countries.**

Crowson CS, Gabriel SE, Semb AG, van Riel PLCM, Karpouzas G, Dessein PH, Hitchon C, Pascual-Ramos V, Kitas GD; Trans-Atlantic Cardiovascular Consortium for Rheumatoid Arthritis, includes van de Laar M and Vonkeman H

**Objectives:** Cardiovascular disease (CVD) risk calculators developed for the general population do not accurately predict CVD events in patients with RA. We sought to externally validate risk calculators recommended for use in patients with RA including the EULAR 1.5 multiplier, the Expanded Cardiovascular Risk Prediction Score for RA (ERS-RA) and QRISK2.
**Methods:** Seven RA cohorts from UK, Norway, Netherlands, USA, South Africa, Canada and Mexico were combined. Data on baseline CVD risk factors, RA characteristics and CVD outcomes (including myocardial infarction, ischaemic stroke and cardiovascular death) were collected using standardized definitions. Performance of QRISK2, EULAR multiplier and ERS-RA was compared with other risk calculators [American College of Cardiology/American Heart Association (ACC/AHA), Framingham Adult Treatment Panel III Framingham risk score-Adult Treatment Panel (FRS-ATP) and Reynolds Risk Score] using c-statistics and net reclassification index.
**Results:** Among 1796 RA patients without prior CVD [mean ( s . d .) age: 54.0 (14.0) years, 74% female], 100 developed CVD events during a mean follow-up of 6.9 years (12430 person-years). Estimated CVD risk by ERS-RA [mean ( s . d .) 8.8% (9.8%)] was comparable to FRS-ATP [mean ( s . d .) 9.1% (8.3%)] and Reynolds [mean ( s . d .) 9.2% (12.2%)], but lower than ACC/AHA [mean ( s . d .) 9.8% (12.1%)]. QRISK2 substantially overestimated risk [mean ( s . d .) 15.5% (13.9%)]. Discrimination was not improved for ERS-RA (c-statistic = 0.69), QRISK2 or EULAR multiplier applied to ACC/AHA compared with ACC/AHA (c-statistic = 0.72 for all) or for FRS-ATP (c-statistic = 0.75). The net reclassification index for ERS-RA was low (-0.8% vs ACC/AHA and 2.3% vs FRS-ATP).
**Conclusion:** The QRISK2, EULAR multiplier and ERS-RA algorithms did not predict CVD risk more accurately in patients with RA than CVD risk calculators developed for the general population.

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Impact factor: 4.818

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Totale impact factor: 18.585
Gemiddelde impact factor: 2.655

Aantal artikelen 1e, 2e of laatste auteur: 7
Totale impact factor: 18.585
Gemiddelde impact factor: 2.655

# Thoraxchirurgie

**1. Supercritical carbon dioxide decellularised pericardium: Mechanical and structural characterisation for applications in cardio-thoracic surgery**
Halfwerk FR, Rouwkema J, Gossen JA, Grandjean JG

**Introduction:** Many biomaterials are used in cardio-thoracic surgery with good short-term results. However, calcification, dehiscence, and formation of scar tissue are reported. The aim of this research is to characterise decellularised pericardium after supercritical carbon dioxide (scCO2) processing as an alternative biological material for uses in cardio-thoracic surgery.
**Methods:** Porcine and bovine pericardium were decellularised using scCO2. Mechanical properties such as tensile strength, elastic modulus, fracture toughness and suture retention strength were determined. Ultrastructure was visualised using Scanning Electron Microscopy. Water uptake and swelling was experimentally determined. Commercially available glutaraldehyde treated bovine pericardium was used as gold standard for comparison.
**Results:** scCO2 decellularised porcine (and bovine pericardium) maintained their tensile strength compared to untreated native pericardium (13.3 +/- 2.4MPa vs 14.0 +/- 4.1MPa, p = 0.73). Tensile strength of glutaraldehyde treated pericardium was significantly higher compared to untreated pericardium (19.4 +/- 7.3MPa vs 10.2 +/- 2.2MPa, p = 0.02). Suture retention strength of scCO2 treated pericardium was significantly higher than glutaraldehyde treated pericardium (p = 0.01). We found no anisotropy of scCO2 or glutaraldehyde treated pericardium based on a trouser tear test. Ultrastructure was uncompromised in scCO2 treated pericardium, while glutaraldehyde treated pericardium showed deterioration of extracellular matrix.
**Conclusion:** scCO2 processing preserves initial mechanical and structural properties of porcine and bovine pericardium, while glutaraldehyde processing damages the extracellular matrix of bovine pericardium. Decellularisation of tissue using scCO2 might give long-term solutions for cardio-thoracic surgery without compromising initial good mechanical properties

Gepubliceerd: J Mech Behav Biomed Mater 2017 Oct 3;77:400-7
Impact factor: 3.110

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**2. A Protocol for Diagnosis and Management of Aortic Atherosclerosis in Cardiac Surgery Patients**
Jansen Klomp WW, Brandon Bravo Bruinsma GJ, Van 't Hof AWJ, Grandjean JG, Nierich AP

In patients undergoing cardiac surgery, use of perioperative screening for aortic atherosclerosis with modified TEE (A-View method) was associated with lower postoperative mortality, but not stroke, as compared to patients operated on without such screening. At the time of clinical implementation and validation, we did not yet standardize the indications for modified TEE and the changes in patient management in the presence of aortic atherosclerosis. Therefore, we designed a protocol, which combined the diagnosis of atherosclerosis of thoracic aorta and the subsequent considerations with respect to the intraoperative management and provides a systematic approach to reduce the risk of cerebral complications

Gepubliceerd: Int J Vasc Med 2017;2017:1874395
Impact factor: 0

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**3. Clinical recognition of acute aortic dissections: insights from a large single-centre cohort study**
Jansen Klomp WW, Brandon Bravo Bruinsma GJ, Peelen LM, Nierich AP, Grandjean JG, van 't Hof AW

**Aims:** Acute aortic dissection (AD) requires immediate treatment, but is a diagnostic challenge. We studied how often AD was missed initially, which patients were more likely to be missed and how this influenced patient management and outcomes.
**Methods:** A retrospective cohort study including 200 consecutive patients with AD as the final diagnosis, admitted to a tertiary hospital between 1998 and 2008. The first differential diagnosis was identified and patients with and without AD included were compared. Characteristics associated with a lower level of suspicion were identified using multivariable logistic regression, and Cox regression was used for survival analyses. Missing data were imputed.
**Results:** Mean age was 63 years, 39% were female and 76% had Stanford type A dissection. In 69% of patients, AD was included in the first differential diagnosis; this was less likely in women (adjusted relative risk [aRR]: 0.66, 95% CI: 0.44-0.99), in the absence of back pain (aRR: 0.51, 95% CI: 0.30-0.84), and in patients with extracardiac atherosclerosis (aRR: 0.64, 95% CI: 0.43-0.96). Absence of AD in the differential diagnosis was associated with the use of more imaging tests (1.8 vs. 2.3, $p = 0.01$) and increased time from admission to surgery (1.8 vs. 10.1 h, $p < 0.01$), but not with a difference in the adjusted long-term all-cause mortality (hazard ratio: 0.76, 95% CI: 0.46-1.27).
**Conclusion:** Acute aortic dissection was initially not suspected in almost one-third of patients, this was more likely in women, in the absence of back pain and in patients

with extracardiac atherosclerosis. Although the number of imaging tests was higher and time to surgery longer, patient outcomes were similar in both groups

Gepubliceerd: Neth Heart J 2017;25(3):200-6
Impact factor: 1.894

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**4. Impact of Modified Transesophageal Echocardiography on Mortality and Stroke after Cardiac Surgery: A Large Cohort Study**
Jansen Klomp WW, Moons CGM, Nierich AP, Brandon Bravo Bruinsma GJ, Van't Hof AWJ, Grandjean JG, Peelen LM

The aim of this study was to investigate the impact of perioperative screening with modified transesophageal echocardiography (A-View method). We compared, in consecutive patients who underwent cardiac surgery between 2006 and 2014, 30-day mortality and in-hospital stroke incidence, operated either with perioperative modified TEE screening (intervention group) or only with conventional TEE screening (control group). Of the 8,605 study patients, modified TEE was applied in 1,391 patients (16.2%). Patients in the intervention group were on average older (71 versus 68 years, $p < 0.001$) and more often females (31.0% versus 28.0%, $p < 0.001$) and had a higher predicted mortality (EuroSCORE I: 5.9% versus 4.0%, $p < 0.001$). The observed 30-day mortality was 2.2% and 2.5% in both groups, respectively, with multivariable and propensity-score adjusted relative risks (RRs) of 0.70 (95% CI: 0.50-1.00, $p = 0.05$) and 0.67 (95% CI: 0.45-0.98, $p = 0.04$). In-hospital stroke was 2.9% and 2.1% in both groups, respectively, with adjusted RRs of 1.03 (95% CI: 0.73-1.45) and 1.01 (95% CI: 0.71-1.43). In patients undergoing cardiac surgery, use of perioperative screening for aortic atherosclerosis with modified TEE was associated with lower postoperative mortality, but not stroke, as compared to patients operated on without such screening

Gepubliceerd: Int J Vasc Med 2017;2017:1857069
Impact factor: 0

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**5. A two site comparison of two point-of-care activated clotting time systems**
Kemna EW, Kuipers C, Oude Luttikhuis-Spanjer AM, Majoor S, Boudrie R, Speekenbrink RG, Hoffman R, Krabbe JG

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Impact factor: 3.432

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Totale impact factor: 8.436
Gemiddelde impact factor: 1.687

Aantal artikelen 1e, 2e of laatste auteur: 1
Totale impact factor: 3.110
Gemiddelde impact factor: 3.110