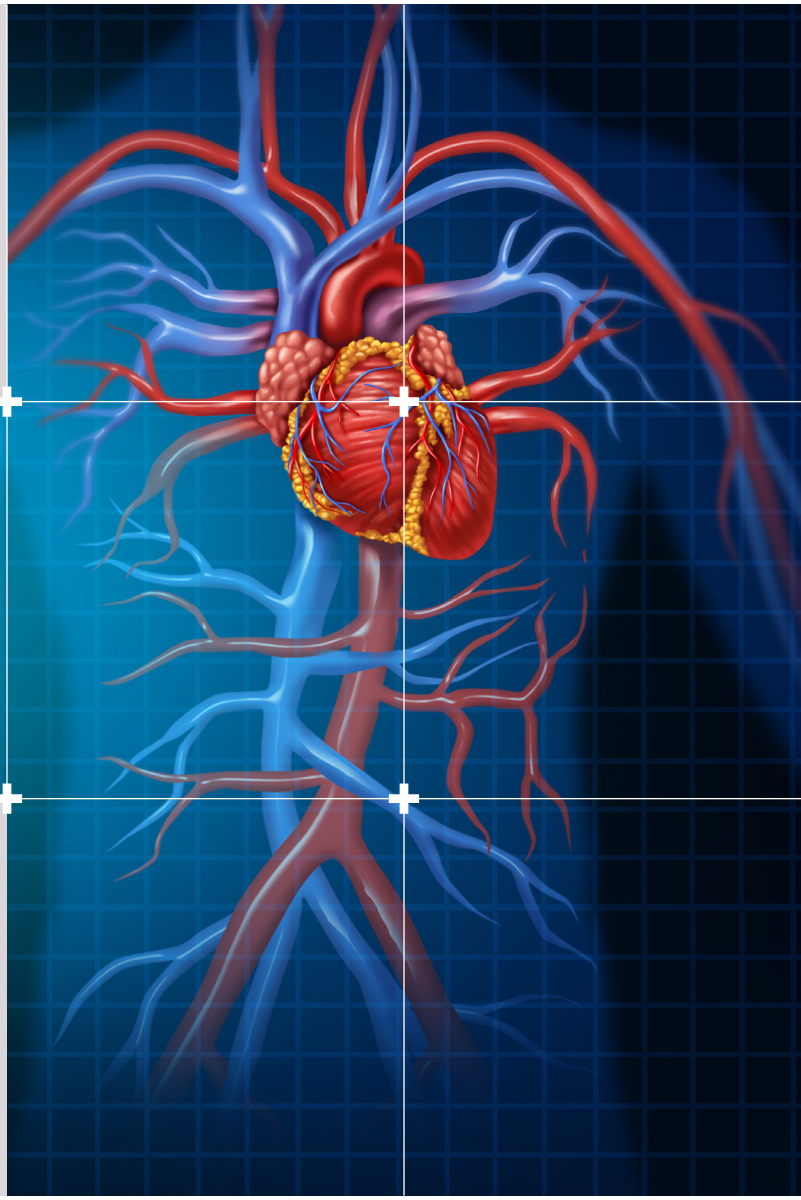
Totstandkoming en methoden
NHG-Standaard CVRM (M84)

Mei 2019



Nederlands
Huisartsen
Genootschap

Inhoudsopgave

1 Samenstelling werkgroep

De NHG-Standaard Cardiovasculair risicomanagement, die tevens wordt uitgebracht als multidisciplinaire richtlijn Cardiovasculair risicomanagement (zie www.richtlijnendatabase.nl), is opgesteld door een multidisciplinaire werkgroep die naast huisartsen bestond uit vertegenwoordigers van diverse andere partijen. De richtlijnontwikkeling werd ondersteund door medewerkers van het Kennisinstituut van de Federatie van Medisch Specialisten en het Nederlands Huisartsen Genootschap.

De werkgroep bestond uit de volgende leden:

- Prof. dr. A.W. (Arno) Hoes, klinisch epidemioloog, werkzaam in het Julius Centrum van het UMC Utrecht te Utrecht (voorzitter)
- Dr.ir. I. (Ineke) van Dis, epidemioloog en voedingswetenschapper, werkzaam bij de Hartstichting te Den Haag
- Y.A. (Yvette) Henstra, verpleegkundig specialist vasculaire geneeskunde, werkzaam in het OVLG te Amsterdam, NVHVV
- Dr. H.M. (Heleen) den Hertog, neuroloog, werkzaam in het Isala Ziekenhuis te Zwolle, NVN
- Dr. K. (Karen) Konings, kaderhuisarts hart- en vaatziekten, werkzaam in huisartsenpraktijk K. Konings en B. van de Rijst te Maastricht, NHG
- H. (Hans) van Laarhoven, manager team collectieve belangenbehartiging, werkzaam bij Harteraad te Den Haag
- Dr. A.H. (AnHo) Liem, cardioloog, werkzaam in het Franciscus Gasthuis & Vlietland te Rotterdam, NVVC
- Dr. F.M.A.C. (Fabrice) Martens, cardioloog, werkzaam in het Deventer Ziekenhuis te Deventer, NVVC
- Prof. dr. Y.M. (Yvo) Smulders, internist-vasculair geneeskundige, werkzaam in het Amsterdam UMC, locatie VUmc te Amsterdam, NIV
- Drs. A. (Anne-Margreet) Strijbis, relatiemanager zorg, werkzaam bij Harteraad te Den Haag, Harteraad
- Drs. J.S. (Judith) Tjin-A-Ton, kaderhuisarts hart- en vaatziekten, werkzaam in huisartsenpraktijk Frakking & Tjin-A-Ton te Amstelveen, NHG
- Prof. dr. F.L.J. (Frank) Visseren, internist-vasculair geneeskundige, werkzaam in het UMC Utrecht te Utrecht, NIV

Met ondersteuning van:

- G.M. (Maike) van Leeuwen, beleid- en projectondersteuner, NIV
- Dr. Tj. (Tjerk) Wiersma, senior-wetenschappelijk medewerker, NHG
- Dr. W. (Wouter) de Ruijter, wetenschappelijk medewerker, NHG tot augustus 2017
- Drs. M. (Martijn) Sijbom, wetenschappelijk medewerker, NHG vanaf augustus 2017
- Dr. I.M. (Iris) Wichers, wetenschappelijk medewerker, NHG
- Dr. B.H. (Bernardine) Stegeman, adviseur, Kennisinstituut van FMS
- Dr. J. (Janneke) Hoogervorst-Schilp, adviseur, Kennisinstituut van FMS tot april 2018
- Dr. A. (Aleid) Wirix, adviseur, Kennisinstituut van FMS vanaf april 2018
- N.F. (Natalia) Bullock, projectsecretaresse, Kennisinstituut van FMS tot januari 2018
- J. (Jill) Heij, junior projectsecretaresse, Kennisinstituut van FMS vanaf februari 2018

2 Algemene achtergrondinformatie

2.1 Doel van de standaard

De multidisciplinaire richtlijn Cardiovasculair risicomanagement (CVRM) c.q. NHG-Standaard CVRM is een update van de richtlijn/standaard uit 2012 over dit onderwerp. Doel is het formuleren van een eenduidig beleid over CVRM dat gevolgd wordt door zowel huisartsen als medisch specialisten.

2.2 Werkwijze

De update van de multidisciplinaire richtlijn en NHG-Standaard geschiedde op initiatief van het Nederlands Huisartsen Genootschap, de Nederlandse Internisten Vereniging en de Nederlandse Vereniging voor Cardiologie. Er werd een multidisciplinaire werkgroep samengesteld, waarin naast huisartsen, internisten en cardiologen, ook vertegenwoordigers van de Harteraad, de Hartstichting, de Nederlandse Vereniging voor Neurologie en de Nederlandse Vereniging voor Hartvaatverpleegkundigen zitting hadden. De werkgroep werd ondersteund door medewerkers van het NHG en het Kennisinstituut van de Federatie Medisch Specialisten.

Uitgangspunt bij de ontwikkeling van de nieuwe richtlijn vormde de richtlijn Cardiovascular disease prevention in clinical practice van de European Society of Cardiology uit 2016 (Atherosclerosis 2016;252:207-74. DOI: 10.1016/j.atherosclerosis.2016.05.037). Deze richtlijn was op het moment van starten de meest recente richtlijn met de meest recente evidence. De werkgroep beoordeelde de aanbevelingen uit deze richtlijn op noodzaak tot revisie. Tevens zijn er knelpunten aangedragen tijdens een Invitational conference door Diabetesvereniging Nederland, IGZ, FMCC, Harteraad (voorheen De Hart&Vaatgroep), KNGF, KNMP, NHG, NVAB, NVALT, NVR, NVVC, Verenso en InEen. De werkgroep stelde vervolgens een lijst met knelpunten op en prioriteerde de knelpunten op basis van: (1) klinische relevantie, (2) de beschikbaarheid van (nieuwe) evidence van hoge kwaliteit, en (3) de te verwachten impact op de kwaliteit van zorg, patiëntveiligheid en (macro)kosten.
Deze Europese richtlijn Cardiovascular disease prevention in clinical practice werd op basis van de lijst van geprioriteerde knelpunten nader uitgewerkt door middel van additionele literatuursearches over specifieke vraagstukken. Daarnaast werd de Richtlijn Cardiovasculair risicomanagement bij (kwetsbare) ouderen integraal opgenomen in deze nieuwe richtlijn CVRM. In onderstaande tabel van noten bij de NHG-Standaard CVRM is aangegeven welke onderbouwing is overgenomen uit de Europese richtlijn, bij welke knelpunten aanvullend is gezocht naar onderbouwende literatuur en welke onderbouwing is overgenomen uit de richtlijn over CVRM bij (kwetsbare) ouderen. Nadere informatie over de gehanteerde zoekstrategieën, onderzoeken die geëxcludeerd werden en de redenen daarvan is te vinden in hoofstuk 3 van dit document. Tabellen waarin de gevonden evidence is samengevat alsmede tabellen waarin de kwaliteit van het gevonden bewijs is beoordeeld zijn te vinden in hoofdstuk 4. Ten slotte werden diverse aanbevelingen uit de Europese richtlijn aangepast om ze geschikt te maken voor de Nederlandse situatie.

Tabel Herkomst noten bij de NHG-Standaard CVRM

Noot 1	Bij wie dient het risico op hart- en vaatziekten te worden geschat?	E
Noot 2	Hoe kan het risico op hart- en vaatziekten worden geschat?	E
Noot 3	Andere voorspellers van het risico op hart- en vaatziekten	E
Noot 4	Coronaire-arteriële-calcium score	K
Noot 5	Body mass index	K
Noot 6	Elektrocardiografie	K
Noot 7	Enkel-armindex	K
Noot 8	Etniciteit	K

Noot 9	Urinezuur	K
Noot 10	Artritis psoriatica	K
Noot 11	COPD	K
Noot 12	Jicht	K
Noot 13	Reumatoïde artritis	K
Noot 14	Ziekte van Bechterew (ankyloserende spondylitis)	K
Noot 15	Hiv	K
Noot 16	IBD	K
Noot 17	Gedragsverandering	E
Noot 18	Psychosociale factoren	E
Noot 19	Sedentaire leefstijl en lichamelijke activiteit	E
Noot 20	Stoppen-met-rokeninterventie	E
Noot 21	Voeding	E
Noot 22	Lichaamsgewicht	E
Noot 23	Leefstijladviezen bij (kwetsbare) ouderen	O
Noot 24	Wat is het advies over het nuchter of niet nuchter bloedprikken in het kader van dyslipidemieën?	E
Noot 25	Streefwaarden van LDL-C	K
Noot 26	Non-HDL-cholesterol	K
Noot 27	Behandeling lipiden	K
Noot 28	Dyslipidemie bij (kwetsbare) ouderen	O
Noot 29	Bloeddrukmeting	K
Noot 30	Wanneer moet een verhoogde bloeddruk medicamenteus behandeld worden?	E
Noot 31	Welke diagnostiek dient te worden gedaan of overwogen bij het starten van bloeddrukmedicatie, bij een zeer sterk verhoogde bloeddruk of een vermoeden van secundaire hypertensie?	E
Noot 32	Welke streefwaarden dienen te worden gehanteerd bij behandeling van een verhoogde bloeddruk?	E
Noot 33	Op welke manier moet een verhoogde bloeddruk behandeld worden?	E
Noot 34	Welke bloeddrukstreefwaarde dienen te worden gehanteerd bij de behandeling van hypertensie bij (kwetsbare) ouderen (> 70 jaar)?	K
Noot 35	Welk type antihypertensivum heeft de voorkeur bij (kwetsbare) ouderen (> 70 jaar) met hypertensie?	K
Noot 36	Wanneer dient gestopt te worden met antihypertensiva bij (kwetsbare) ouderen (> 70 jaar)?	K
Noot 37	Antitrombotische therapie bij personen zonder hart- en vaatziekten	E
Noot 38	Wanneer dient men te starten met trombocytenaggregatieremmers (waaronder acetylsalicylzuur) bij (kwetsbare) ouderen (> 70 jaar)?	K
Noot 39	Wanneer dient men te stoppen met trombocytenaggregatieremmers (waaronder acetylsalicylzuur) bij (kwetsbare) ouderen (> 70 jaar)?	K
Noot 40	Therapietrouw	E
Noot 41	Atriumfibrilleren	E
Noot 42	Ischemische hartziekten	E
Noot 43	Chronisch hartfalen	E
Noot 44	Cerebrovasculaire aandoeningen	E
Noot 45	Perifeer arterieel vaatlijden	E

Noot 46	Waar te interveniëren; zorgsettings en betrokkenen	E
Noot 47	Organisatie van zorg bij (kwetsbare) ouderen	O
Noot 48	Interventies op populatieniveau	E
Noot 49	Totstandkoming risicotabel CVRM 2018	K

E = afkomstig uit Europese richtlijn, K = nader uitgewerkt op basis van knelpuntenanalyse, O = overgenomen uit richtlijn over (kwetsbare) ouderen.

Nadat de werkgroep de conceptrichtlijn had opgesteld, volgde in het voorjaar van 2018 een uitgebreide externe commentaarronde. Daarbij werd commentaar ontvangen van De Hartstichting, Harteraad, KNGF, KNMP, Lareb, NDF, VIG, NHG, NIV, NVALT, NVD, NVHVV, NVKC, NVKG, NVN, NVR, NVVC, NVVG, NVvH, NVvP, NVZ, V&VN, ZINL, ZN, InEen, Voedingscentrum, DCN, Werkgroep CNS en HartVaatHAG. De ontvangen commentaren resulteerden in diverse aanpassingen van de richtlijn.
Eind 2018 werd de bijgestelde richtlijn ter autorisatie aangeboden aan de verenigingen die betrokken waren bij het opstellen van de richtlijn en een aantal andere belangrijke stakeholders. Alle deelnemende partijen autoriseerden de richtlijn: NHG, NIV, NVVC, NVHVV, Harteraad, Hartstichting en NVN. Daarnaast werd de richtlijn geautoriseerd door NVKG, NVKC, V&VN, NVR, KNGF, NVD en VHNL.

2.3 Gebruikers van de richtlijn

De richtlijn is primair bedoeld voor alle hulpverleners die zich bezighouden met de herkenning en begeleiding van mensen met een verhoogd risico op hart- en vaatziekten.

2.4 Betrokkenheid patiëntenvertegenwoordigers

Het patiëntenperspectief werd gewaarborgd door de Harteraad, die met twee personen was vertegenwoordigd in de werkgroep.

2.5 Presentatie

Door de multidisciplinaire totstandkoming van deze richtlijn is de opbouw enigszins afwijkend van de gebruikelijke opbouw van standaarden. De richtlijn volgt in grote lijnen de opbouw van de Europese richtlijn. Meer details en informatie over achtergronden en onderbouwing is te vinden in de noten.

2.6 Implementatie

Ter bevordering van de implementatie van de richtlijn door huisartsen gaat de NHG-Standaard CVRM vergezeld van een Praktische Handleiding (zie *www.nhg.org*) waarin met name de medicamenteuze behandelingsadviezen en de laboratoriumbepalingen die worden geadviseerd bij mensen die onder behandeling zijn voor CVRM, nader zijn uitgewerkt.

2.7 Juridische status van richtlijnen

Richtlijnen bevatten geen wettelijke voorschriften, maar aanbevelingen die zo veel mogelijk op bewijs gebaseerd zijn. Zorgverleners kunnen aan de aanbevelingen voldoen in het streven om kwalitatief goede of ‘optimale’ zorg te verlenen. Aangezien deze aanbevelingen gebaseerd zijn op ‘algemeen bewijs voor optimale zorg’ en de inzichten van de werkgroep hierover, kunnen zorgverleners op basis van hun professionele autonomie zo nodig in individuele gevallen afwijken van de richtlijn. Afwijken van richtlijnen is, als de situatie van de patiënt dat vereist, zelfs noodzakelijk. Wanneer van deze richtlijn wordt afgeweken, wordt het aanbevolen om dit beargumenteerd en gedocumenteerd, waar relevant in overleg met de patiënt, te doen.

Inbreng van de patiënt

De NHG-Standaarden geven richtlijnen voor het handelen van de huisarts; de rol van de huisarts staat dan ook centraal. Daarbij geldt echter altijd dat factoren van de kant van de patiënt het beleid mede bepalen. Om praktische redenen komt dit uitgangspunt niet telkens opnieuw in de richtlijn aan de orde, maar wordt het hier

expliciet vermeld. De huisarts stelt waar mogelijk het beleid vast in samenspraak met de patiënt, met inachtneming van diens specifieke omstandigheden en met erkenning van diens eigen verantwoordelijkheid, waarbij adequate voorlichting een voorwaarde is.

Afweging door de huisarts
Het persoonlijk inzicht van de huisarts is uiteraard bij alle richtlijnen een belangrijk aspect. Afweging van de relevante factoren in de concrete situatie kan beredeneerd afwijken van het hierna beschreven beleid rechtvaardigen. Dat laat onverlet dat deze standaard bedoeld is om te fungeren als maat en houvast.

2.8 Delegeren van taken

NHG-Standaarden bevatten richtlijnen voor huisartsen. Dit betekent niet dat de huisarts alle genoemde taken persoonlijk moet verrichten. Sommige taken kunnen worden gedelegeerd aan de praktijkassistente, praktijkondersteuner of praktijkverpleegkundige, mits zij worden ondersteund door duidelijke werkafspraken, waarin wordt vastgelegd in welke situaties de huisarts moet worden geraadpleegd en mits de huisarts toeziet op de kwaliteit. Omdat de feitelijke keuze van de te delegeren taken sterk afhankelijk is van de lokale situatie, bevatten de standaarden daarvoor geen concrete aanbevelingen.

2.9 Belangenverstrengeling

Alle werkgroepleden hebben een KNAW Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling ingevuld. De vermelde gegevens staan hieronder samengevat.

De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van het Kennisinstituut van de Federatie Medisch Specialisten.

Werkgroeplid	Functie	Nevenfuncties	Gemelde belangen	Ondernomen actie
Hoes (voorzitter)	- Hoogleraar Klinische Epidemiologie & Huisartsengeneeskunde - Voorzitter/medisch manager, divisie Julius Centrum voor Gezondheidswetenschappen en Eerstelijns Geneeskunde, UMC Utrecht - Voorzitter/medisch manager a.i., divisie Interne Geneeskunde en Dermatologie, UM Utrecht (tot juni 2017)	- Lid College ter Beoordeling van Geneesmiddelen, Ministerie van VWS (betaalde functie honorarium) (tot oktober 2016) - Lid Board Heart Failure Association, European Society of Cardiology (ESC) (onbetaald) (tot september 2018) - Lid Board European Association for Preventive Cardiology, ESC (onbetaald) - Lid Editorial Board European Journal of Heart Failure (onbetaald) - Lid Editorial Board ESC Heart Failure (onbetaald) - Lid commissie Zorg Binnen Bereik, een stichting, met als private partners Achmea en Philips, die tot doel heeft zorgplatforms voor chronische ziekten (hartfalen, COPD en diabetes) te ontwikkelen en te implementeren om zelfzorg te bevorderen. (onbetaald) (tot oktober 2016) - Medevoorzitter Task Force Guidelines Prevention of Cardiovascular Disease in Clinical Practice (ESC) (onbetaald) - Voorzitter Council for Cardiovascular Primary Care van de ESC (onbetaald) (tot september 2018) - Lid visitatiecommissie Inspectie voor de Gezondheidszorg (betaald) (tot juni 2016) - Lid Board European Primary Care Cardiovascular Society (onbetaald) (tot december 2017) - Lid Raad van Toezicht namens UMC Utrecht van Stichting HUB (stichting die organoïden ontwikkelt) (onbetaald)	-	Geen
Konings	Kaderhuisarts hart- en vaatziekten	-	-	Geen
Tjin-A-Ton	Kaderhuisarts hart- en vaatziekten	- Huisartsopleider VUMC	-	Geen
Visseren	- Hoogleraar Vasculaire geneeskunde - Opleider Vasculaire geneeskunde	- Lid sectie Vasculaire geneeskunde, deelspecialisme NIV - Werkgroeplid van de werkgroepen (erfelijke) dyslipidemie in de tweede en derde lijn en het addendum (kwetsbare) ouderen bij de CVRM-richtlijn	Deelname aan fase II en II multicenter trials over PSCK9-antilichamen; betrokken bij	Geen

			patiëntenінclusie, geen data-analyse	
Smulders	- Hoogleraar Interne Geneeskunde - Opleider Interne Geneeskunde	- Adjunct-hoofdredacteur Nederlands Tijdschrift voor Geneeskunde - Lid beoordelingscommissies ZonMw	-	Geen
Liem	- Cardioloog - Opleider	- Ontwikkeling onderwijsmodules NVVC - Werkgroeplid van de werkgroep (erfelijke) dyslipidemie in de tweede en derde lijn	Advies aan universiteiten en industrie over dyslipidemie en lipidenverlaende middelen	Geen actie; advies over alle middelen
Martens	Cardioloog	Bestuurslid Werkgroep Cardiologische centra Nederland (WCN)	Advies aan universiteiten en industrie over dyslipidemie en lipidenverlaende middelen	Geen actie; advies over alle middelen
Den Hertog	Neuroloog	- Lid werkgroep regionaal CVRM Thoon (huisartsen) - Projectleider Benefietconsortium Hartstichting	-	Geen
Henstra	Verpleegkundig Specialist Vasculaire geneeskunde		Advies aan industrie lancering nieuwe medicatie bij FH	Geen; valt buiten het bestek van de richtlijn
Strijbis	Relatiemanager Harteraad	Werkgroeplid Hypertensie in de tweede en derde lijn	-	Geen
Van Laarhoven	- Manager Team Collectieve belangenbehartiging Harteraad - Beleidsadviseur Harteraad - Waarnemend directeur Harteraad	Werkgroeplid (erfelijke) dyslipidemie in de tweede en derde lijn	-	Geen
Van Dis	- Beleidsadviseur Hartstichting	Lid van de werkgroep Voeding van de European Heart Network	Hartstichting heeft een samenwerkingscontract met Unilever	Geen

Financiering

De totstandkoming van deze richtlijn is gefinancierd door het Nederlands Huisartsen Genootschap en de Stichting Kwaliteitsgelden Medisch Specialisten (SKMS).

3 Zoekstrategiën en exclusietabellen

Onderstaand een overzicht van de gebruikte zoekstrategieën en exclusietabellen bij de noten bij de NHG-Standaard, voor zover deze niet uit de Europese richtlijn zijn overgenomen. Van noten die wel op de Europese richtlijn berusten zijn deze gegevens niet beschikbaar.

Noot 4: Coronaire-arteriële-calcium score

Zoekverantwoording

Database	Zoektermen	Totaal
Medline (PubMed) 2005-feb 2017 Engels, Nederlands	(CAC(tiab) OR coronary calcium score(tiab) OR calcium score(tiab) OR coronary artery calcium(tiab) OR coronary arterial calcium(tiab) OR coronary artery calcification(tiab) OR coronary arterial calcification(tiab) OR coronary calcification(tiab) OR coronary computed tomographic angiography(tiab) OR CCTA(tiab)) AND (cardiovascular diseases/epidemiology(mj) OR cardiovascular diseases/mortality(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR reclassification(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR risk(ti) OR mortality(tiab)) AND (meta-anal*(tiab) OR systematic(sb) OR random*(tiab) OR RCT(tiab) OR review(pt))	257

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Exclusie. Narrative review.	Sathiyakumar V, Blumenthal RS, Nasir K, Martin SS. Addressing Knowledge Gaps in the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: a Review of Recent Coronary Artery Calcium Literature. Current atherosclerosis reports 2017;19:7.
Exclusie. Narrative review.	Osawa K, Nakanishi R, Budoff MJ. Is there a role for coronary artery calcification scoring in primary prevention of cerebrovascular disease? Atherosclerosis 257:279-287.
Exclusie. Narrative review.	Osawa K, Nakanishi R, Budoff M. Coronary Artery Calcification. Glob Heart 2016;11:287-93.
Exclusie. Narrative review.	Kianoush S, Rifai MA, Cainzos-Achirica M, Umapathi P, Graham G, Blumenthal RS, et al. An Update on the Utility of Coronary Artery Calcium Scoring for Coronary Heart Disease and Cardiovascular Disease Risk Prediction. Current atherosclerosis reports 2016;18:13.
Exclusie. Alleen laagrisicovrouwen	Kavousi M, Desai CS, Ayers C, Blumenthal RS, Budoff MJ, Mahabadi AA, et al. Prevalence and Prognostic Implications of Coronary Artery Calcification in Low-Risk Women: A Meta-analysis. JAMA 2016;316:2126-34.
Exclusie. Narrative review, alleen MESA study.	Blaha MJ, Yeboah J, Rifai MA, Liu K, Kronmal R, Greenland P. Providing Evidence for Subclinical CVD in Risk Assessment. Glob Heart 2016;11:275-85.
Exclusie. Narrative review.	Bambrick P, Tan WS, Mulcahy R, Pope GA, Cooke J. Vascular risk assessment in older adults without a history of cardiovascular disease. Experimental gerontology 2016;79:37-45.
Exclusie. Narrative review.	Zeb I, Budoff M. Coronary artery calcium screening: does it perform better than other cardiovascular risk stratification tools? International journal of molecular sciences. 2015;16:6606-20.
Exclusie. Vergelijking CAC met MPI (myocardial perfusion imaging).	Yuoness SA, Goha AM, Romsa JG, Akincioglu C, Warrington JC, Datta S, et al. Very high coronary artery calcium score with normal myocardial perfusion SPECT imaging is associated with a moderate incidence of severe coronary artery disease. Eur J Nucl Med Mol Imaging 2015;42:1542-50.
Exclusie. Narrative review.	Weber LA, Cheezum MK, Reese JM, Lane AB, Haley RD, Lutz MW, et al. Cardiovascular Imaging for the Primary Prevention of Atherosclerotic Cardiovascular Disease Events. Curr Cardiovasc Imaging Rep 2015;8:36.

Exclusie. Narrative review.	Thomas DM, Divakaran S, Villines TC, Nasir K, Shah NR, Slim AM, et al. Management of Coronary Artery Calcium and Coronary CTA Findings. Curr Cardiovasc Imaging Rep 2015;8:18.
Exclusie. SR voor CRP en CAC met search tot aug 2015. Alleen AUC's, geen reclassificatie.	Qureshi WT, Rana JS, Yeboah J, Nasir UB, Al-Mallah MH. Risk Stratification for Primary Prevention of Coronary Artery Disease: Roles of C-Reactive Protein and Coronary Artery Calcium. Current cardiology reports 2015;17:110.
Inclusie. Dallas Heart Study, met meta-analyse van NRI's, zoekdatum dec 2014.	Paixao AR, Ayers CR, Sabbagh AE, Sanghavi M, Berry JD, Rohatgi A, et al. Coronary Artery Calcium Improves Risk Classification in Younger Populations. JACC Cardiovascular imaging 2015;8:1285-93.
Exclusie. Narrative review.	Manson JE, Bassuk SS. Biomarkers of cardiovascular disease risk in women. Metabolism: clinical and experimental 2015;64:S33-9.
Exclusie. Narrative review en study design Koreaanse studie.	Lee JH, B OH, Han D, Park HE, Choi SY, Sung J, et al. Reassessing the Usefulness of Coronary Artery Calcium Score among Varying Racial and Ethnic Groups by Geographic Locations: Relevance of the Korea Initiatives on Coronary Artery Calcification Registry. Journal of cardiovascular ultrasound 2015;23:195-203.
Exclusie. Narrative review.	Joshi PH, Nasir K. Discordance between Risk Factors and Coronary Artery Calcium: Implications for Guiding Treatment Strategies in Primary Prevention Settings. Progress in cardiovascular diseases 2015;58:10-8.
Exclusie. Narrative review.	Degrell P, Sorbets E, Feldman LJ, Steg PG, Ducrocq G. Screening for coronary artery disease in asymptomatic individuals: Why and how? Arch Cardiovasc Dis 2015;108:675-82.
Exclusie. Narrative review.	Wallace ML, Ricco JA, Barrett B. Screening strategies for cardiovascular disease in asymptomatic adults. Primary care 2014;41:371-97.
Exclusie. Narrative review.	Blaha MJ, Silverman MG, Budoff MJ. Is there a role for coronary artery calcium scoring for management of asymptomatic patients at risk for coronary artery disease?: Clinical risk scores are not sufficient to define primary prevention treatment strategies among asymptomatic patients. Circulation Cardiovascular imaging 2014;7:398-408; discussion.
Niet voltekst beoordeeld.	Anthony D, George P, Eaton CB. Cardiac risk factors: noninvasive testing to detect coronary heart disease. FP Essent 2014;421:21-7.
Exclusie. Narrative review.	Akhabue E, Thiboutot J, Cheng JW, Vittorio TJ, Christodoulidis G, Grady KM, et al. New and emerging risk factors for coronary heart disease. The American journal of the medical sciences 2014;347:151-8.
Exclusie. Narrative review.	Wachira JK, Stys TP. Cardiovascular disease and bridging the diagnostic gap. South Dakota medicine: the journal of the South Dakota State Medical Association 2013;66(9):366-9.
Exclusie. Narrative review.	Wierzbicki AS. New directions in cardiovascular risk assessment: the role of secondary risk stratification markers. International journal of clinical practice 2012;66:622-30.
Exclusie. SR, alleen PubMed, geen zoek- en selectieverantwoording.	Vliegenthart R, Morris PB. Computed tomography coronary artery calcium scoring: review of evidence base and cost-effectiveness in cardiovascular risk prediction. Journal of thoracic imaging 2012;27:296-303.
Exclusie. Narrative review.	Shah NR, Coulter SA. An evidence-based guide for coronary calcium scoring in asymptomatic patients without coronary heart disease. Texas Heart Institute journal/from the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital 2012;39:240-2.
Exclusie. Narrative review.	Sekikawa A, Curb JD, Edmundowicz D, Okamura T, Choo J, Fujiyoshi A, et al. Coronary artery calcification by computed tomography in epidemiologic research and cardiovascular disease prevention. Journal of epidemiology/Japan Epidemiological Association 2012;22:188-98.
Exclusie. Wel SR, maar composite intervention (div.	Rodondi N, Auer R, Sulzer VdB, Ghali WA, Cornuz J. Atherosclerosis screening by noninvasive imaging for cardiovascular prevention: a systematic review. Journal of general internal medicine 2012;27:220-31.

'atherosclerosis screening' methods)	
Inclusie. SR tot 7-9-2011, golden hit (en recenter dan de andere Peters 2011)	Peters SA, Ruijter HMd, Bots ML, Moons KG. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart (British Cardiac Society) 2012;98:177-84.
Exclusie. SR tot 1-2-2011, golden hit, maar andere Peters 2011 is recenter	Peters SA, Bakker M, Ruijter HMd, Bots ML. Added value of CAC in risk stratification for cardiovascular events: a systematic review. European journal of clinical investigation 2012;42:110-6.
Exclusie. Narrative review. Wel mooie summary Table 1 (tot en met 2010)	Nasir K, Clouse M. Role of nonenhanced multidetector CT coronary artery calcium testing in asymptomatic and symptomatic individuals. Radiology 2012;264:637-49.
Exclusie. Narrative review.	Erbel R, Budoff M. Improvement of cardiovascular risk prediction using coronary imaging: subclinical atherosclerosis: the memory of lifetime risk factor exposure. European heart journal 2012;33:1201-13.
Exclusie. Narrative review.	Budoff MJ. Screening for Ischemic Heart Disease with Cardiac CT: Current Recommendations. Scientifica 2012;2012:812046.
Exclusie. Narrative review.	Wilson SR, Lin FY, Min JK. Role of coronary artery calcium score and coronary CT angiography in the diagnosis and risk stratification of individuals with suspected coronary artery disease. Current cardiology reports 2011;13:271-9.
Niet verkrijgbaar.	Mehra S, Movahed H, Movahed A. Coronary artery calcium scoring. Reviews in cardiovascular medicine 2011;12:e94-e103.
Exclusie. Narrative review.	Hecht HS. Coronary artery calcium: utilization for primary prevention of CHD. Current cardiology reports 2011;13(6):465-74.
Exclusie. Narrative review, verslag van guideline-revision.	Budoff MJ, Malpeso JM. Is coronary artery calcium the key to assessment of cardiovascular risk in asymptomatic adults? Journal of cardiovascular computed tomography 2011;5:12-5.
Exclusie. Narrative review.	Sharma RK, Sharma RK, Voelker DJ, Singh VN, Pahuja D, Nash T, et al. Cardiac risk stratification: role of the coronary calcium score. Vascular health and risk management 2010;6:603-11.
Exclusie. Narrative review.	Patel AA, Budoff MJ. Screening for heart disease: C-reactive protein versus coronary artery calcium. Expert review of cardiovascular therapy 2010;8:125-31.
Exclusie. Narrative review.	Orringer CE. The absence of coronary calcium: clinical and therapeutic implications for the clinical lipidologist. Journal of clinical lipidology 2010;4:472-7.
Exclusie; wel een SR; geen definitie van CAC + versus CAC -; geen reclassificatie	Rennenberg RJ, Kessels AG, Schurgers LJ, Engelshoven JMv, Leeuw PWd, Kroon AA. Vascular calcifications as a marker of increased cardiovascular risk: a meta-analysis. Vascular health and risk management 2009;5:185-97.
Niet voltekst beoordeeld.	Pessana F, Armentano R, Chironi G, Megnien JL, Mousseaux E, Simon A. Subclinical atherosclerosis modeling: Integration of coronary artery calcium score to Framingham equation. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual Conference 2009;2009:5348-51.
Exclusie; SR uit 2009, alleen MEDLINE. Recentere SR beschikbaar (Peters 2012)	Helfand M, Buckley DI, Freeman M, Fu R, Rogers K, Fleming C, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Annals of internal medicine 2009;151:496-507.
Exclusie. Clinical guideline	Using nontraditional risk factors in coronary heart disease risk assessment: U.S. Preventive Services Task Force recommendation statement. Annals of internal medicine 2009;151:474-82.

Exclusie. Narrative review.	Raggi P, Shaw LJ. Epidemiologic guidance with coronary artery calcium scoring. Current cardiology reports 2008;10:60-6.
Exclusie. Narrative review.	Raggi P, Khan A, Arepali C, Stillman AE. Coronary artery calcium scoring in the age of CT angiography: what is its role? Current atherosclerosis reports 2008;10:438-43.
Exclusie. Narrative review.	Elkeles R. Computed tomography imaging, coronary calcium and atherosclerosis. Expert review of cardiovascular therapy 2008;6:1083-93.
Exclusie. Narrative review.	Budoff MJ, Gul KM. Expert review on coronary calcium. Vascular health and risk management 2008;4:315-24.
Exclusie. Narrative review; wel poging SR, geen zoekverantwoording.	Simon A, Chironi G, Levenson J. Comparative performance of subclinical atherosclerosis tests in predicting coronary heart disease in asymptomatic individuals. European heart journal 2007;28:2967-71.
Exclusie. Wel SR, maar alleen over betekenis CAC-score zero.	Shareghi S, Ahmadi N, Young E, Gopal A, Liu ST, Budoff MJ. Prognostic significance of zero coronary calcium scores on cardiac computed tomography. Journal of cardiovascular computed tomography 2007;1:155-9.
Exclusie. Wel SR, maar over CAC-score bij mannen versus vrouwen.	Bellasi A, Lacey C, Taylor AJ, Raggi P, Wilson PW, Budoff MJ, et al. Comparison of prognostic usefulness of coronary artery calcium in men versus women (results from a meta- and pooled analysis estimating all-cause mortality and coronary heart disease death or myocardial infarction). The American journal of cardiology 2007;100:409-14.
Exclusie. SR, geen reclassificatie.	Ardehali R, Nasir K, Kolandaivelu A, Budoff MJ, Blumenthal RS. Screening patients for subclinical atherosclerosis with non-contrast cardiac CT. Atherosclerosis 2007;192:235-42.
Exclusie. SR, geen reclassificatie.	Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G. The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review. Health technology assessment (Winchester, England) 2006;10:iii-iv, ix-x, 1-41.
Exclusie. Narrative review.	Thompson JB, Rivera JJ, Blumenthal RS, Danyi P. Primary prevention for patients with intermediate Framingham risk scores. Current cardiology reports 2006;8:261-6.
Exclusie. Narrative review.	Simon A, Chironi G, Levenson J. Performance of subclinical arterial disease detection as a screening test for coronary heart disease. Hypertension 2006;48:392-6.
Exclusie. Narrative review.	Thompson BH, Stanford W. Update on using coronary calcium screening by computed tomography to measure risk for coronary heart disease. The international journal of cardiovascular imaging 2005;21:39-53.
Exclusie. Narrative review.	Raggi P, Ferramosca E, Bellasi A, Ratti C. Coronary artery calcium screening: implications for clinical practice. Future cardiology 2005;1:215-23.
Exclusie. Narrative review.	Raggi P, Berman DS. Computed tomography coronary calcium screening and myocardial perfusion imaging. Journal of nuclear cardiology: official publication of the American Society of Nuclear Cardiology 2005;12:96-103.

Noot 5: Body mass index (BMI)

Zoekverantwoording

Database	Zoektermen	Totaal
Medline (PubMed) 2005-apr 2017 Engels, Nederlands	(cardiovascular diseases/epidemiology(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (meta-analysis(pt) OR meta-anal*(tiab) OR systematic(sb) OR systematic review(ti)) AND (body mass index(mh) OR body mass index(ti) OR BMI(ti)) – LH/NHG Cohort-studies (cardiovascular diseases/epidemiology(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (cohort studies(mh) OR cohort study(tiab)) AND (body mass index(mh) OR body mass index(ti) OR BMI(ti)) – LH/NHG	172 SR 317 cohort

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Hernesniemi, 2015	Reclassificerende waarde van interactie tussen risicofactoren (onder andere BMI), niet van BMI apart
Simmonds, 2015	O: obesitas op latere leeftijd
Chen, 2013	BMI als onafhankelijke variabele
Tsukinoki, 2012	BMI als onafhankelijke variabele
Friedemann, 2012	P: kinderen. O: CVD risicoparameters
Yatsuya, 2010	BMI als onafhankelijke variabele
Cameron, 2009	BMI als onafhankelijke variabele
Ionnidis, 2009	Genetische markers associatie met CVD
Hernesniemin, 2015	Match met SR

Noot 6: Electrocardiografie

Zoekverantwoording

Systematische reviews/meta-analyse

Database	Zoektermen	Totaal
Medline (PubMed) 2005-april 2017 Engels, Nederlands	(cardiovascular diseases(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalenceti)) AND (meta-analysis(pt) OR meta-anal*(tiab) OR systematic(sb) OR systematic review(ti)) AND (electrocardiography(mh) OR electrocardiograph*(tiab) OR ECG(tiab))	484

Observationeel onderzoek

Database	Zoektermen	Totaal
Medline (PubMed) 2011-juli 2017 Engels, Nederlands	(((cardiovascular diseases(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR risk stratification(tiab) OR mortality(tiab) OR incidence(ti) OR prevalence(ti) OR screening(ti)) AND (reclassification(all fields) OR NRI(tiab) OR prediction model(tiab)) AND (electrocardiography(mh) OR electrocardiograph*(tiab) OR ECG(tiab)) AND (hasabstract(text) AND ("2011/01/01"(PDat) : "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))) NOT ((cardiovascular diseases(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (meta-analysis(pt) OR meta-anal*(tiab) OR systematic(sb) OR systematic review(ti)) AND (electrocardiography(mh) OR electrocardiograph*(tiab) OR ECG(tiab)) AND (hasabstract(text) AND ("2005/01/01"(PDat) : "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))) AND (hasabstract(text) AND ("2011/01/01"(PDat) : "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))) OR ((((CVD(tiab) OR cardiovascular disease(tiab) OR cardiovascular event*(tiab) OR vascular disease(tiab) OR vascular event*(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR risk stratification(tiab) OR mortality(tiab) OR incidence(ti) OR prevalence(ti) OR screening(ti)) AND (cohort studies(mh) OR follow-up stud*(tiab) OR longitudinal stud*(tiab) OR cohort stud*(tiab)) AND (electrocardiography(mh) OR electrocardiograph*(tiab) OR ECG(tiab) OR electrocardiogram(tiab)) AND (hasabstract(text) AND ("2011/01/01"(PDat) : "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))) NOT ((cardiovascular diseases(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular	544

	disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (meta-analysis(pt) OR meta-anal*(tiab) OR systematic(sb) OR systematic review(ti)) AND (electrocardiography(mh) OR electrocardiograph*(tiab) OR ECG(tiab)) AND (hasabstract(text) AND ("2005/01/01"(PDat) : "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))) AND (hasabstract(text) AND ("2011/01/01"(PDat) : "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))) NOT (((cardiovascular diseases(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR risk stratification(tiab) OR mortality(tiab) OR incidence(ti) OR prevalence(ti) OR screening(ti)) AND (randomized controlled trial(pt) OR random*(tiab) OR RCT(tiab)) AND (electrocardiography(mh) OR electrocardiograph*(tiab) OR ECG(tiab)) AND (hasabstract(text) AND ("2011/01/01"(PDat) : "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))) NOT ((cardiovascular diseases(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (meta-analysis(pt) OR meta-anal*(tiab) OR systematic(sb) OR systematic review(ti)) AND (electrocardiography(mh) OR electrocardiograph*(tiab) OR ECG(tiab)) AND (hasabstract(text) AND ("2005/01/01"(PDat) : "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))) AND (hasabstract(text) AND ("2011/01/01"(PDat) : "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))) AND (hasabstract(text) AND ("2011/01/01"(PDat) : "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))) AND (hasabstract(text) AND ("2011/01/01"(PDat) : "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))	

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Chou, 2011	Systematische review, geen van de onderzoeken berekende de NRI
Hadaegh, 2012	Alleen inclusie van vrouwen
Badheka, 2013	Eerdere versie van het onderzoek van Shah et al. (Shah, 2016)
de Groot, 2015	Geen NRI voor gecombineerde ecg-afwijkingen
Waks, 2016	Andere uitkomstmaat (plotselinge hartdood)

Noot 7: Enkel-armindex

Zoekverantwoording

Systematische reviews/meta-analyse

Database	Zoektermen	Totaal
PubMed	(cardiovascular diseases(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (meta-analysis(pt) OR meta-anal*(tiab) OR systematic(sb) OR systematic review(ti)) AND (ankle brachial index(mh) OR ankle brachial index(tiab)) AND (hasabstract(tekst) AND ("2005/01/01"(PDat): "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))	96

Observationeel onderzoek vanaf augustus 2012

Database	Zoektermen	Totaal
PubMed	((cardiovascular diseases(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (randomized controlled trial(pt) OR random*(tiab) OR RCT(tiab) OR cohort studies(mh) OR cohort study(tiab)) AND (ankle brachial index(mh) OR ankle brachial index(tiab)) AND (hasabstract(tekst) AND ("2012/08/01"(PDat): "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))) NOT ((cardiovascular diseases(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (meta-analysis(pt) OR meta-anal*(tiab) OR systematic(sb) OR systematic review(ti)) AND (ankle brachial index(mh) OR ankle brachial index(tiab)) AND (hasabstract(tekst) AND ("2005/01/01"(PDat): "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))) AND (hasabstract(text) AND ("2012/08/01"(PDat) : "3000/12/31"(PDat)) AND (English(lang) OR Dutch(lang)))	459

Exclusietabel

Auteur en jaartal	Redenen van exclusie
U.S. Preventive Services Task Force, 2009	Oudere systematische review van de US Preventive Task Force naar het gebruik van niet-klassieke risicofactoren bij asymptomatische personen
Helfand, 2009	Oudere systematische review van de US Preventive Task Force naar het gebruik van niet-klassieke risicofactoren in de intermediaire risicogroep op hart- en vaatziekten
Van Kempen, 2016	Kosteneffectiviteitsanalyse
Moyer, 2013	Beschrijving van de systematische review van Lin (2013)
Fowkes, 2008	Samenwerkingsverband van cohorten die waren geïncludeerd in de systematische review van Lin (2013)
Heald, 2006	Systematische review naar associatie van ABI

Noot 8: Etniciteit

Zoekverantwoording

Database	Zoektermen	Totaal
Medline (PubMed) 2005-april 2017 Engels, Nederlands	(cardiovascular diseases/epidemiology(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (meta-analysis(pt) OR meta-anal*(tiab) OR systematic(sb) OR systematic review(ti)) AND (minority health(mh) OR ethnic groups(tiab) OR ethnic population*(tiab) OR minority groups(tiab) AND minority population*(tiab) OR ethnicity(tiab) OR multi-ethnic(tiab) OR moroccan(ti) OR Turkish(ti) OR Surinamese(ti) OR Antillean(ti) OR asian*(ti) OR african*(ti))	222
Medline (PubMed) 2005-sep 2017	((cardiovascular diseases(mj) OR CVD(tiab) OR cardiovascular(tiab) OR vascular disease(tiab) OR vascular event*(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (reclassification(tiab) OR predict*(tiab) OR stratification(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR risk characteristics(tiab) OR risk estimation(tiab) OR risk evaluation(tiab) OR	156

Engels, Nederlands	increased risk(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (randomized controlled trial(pt) OR random*(tiab) OR RCT(tiab) OR cohort studies(mh) OR cohort study(tiab)) AND (minority health(mh) OR ethnic*(tiab) OR race(ti) OR minority groups(tiab) OR minority population*(tiab) OR ethnicity(tiab) OR multi-ethnic(tiab) OR moroccan(ti) OR Turkish(ti) OR Surinamese(ti) OR Antillean(ti) OR asian*(ti) OR african*(ti))) AND (Framingham(tiab) OR QRISK*(tiab) OR risk estimation(tiab) OR coronary risk(tiab) OR risk evaluation(tiab))	

Exclusietabel

Op basis van titel en abstract werden in eerste instantie twee studies voorgeselecteerd. Na raadpleging van de volledige tekst werden vervolgens geen studies geëxcludeerd. Daarom wordt geen exclusietabel weergegeven.

Noot 9: Urinezuur

Zoekverantwoording

Database	Zoektermen	Totaal
Medline (PubMed) 2005-feb 2017	((uric acid(mj) OR serum uric acid(tiab) OR uric acid level*(tiab) OR uric acid value*(tiab) OR increased uric acid(tiab) OR hyperuricemia(tiab) OR elevated uric acid(tiab)) AND (cardiovascular diseases/epidemiology(mj) OR cardiovascular diseases/etiology(mj) OR cardiovascular diseases/mortality(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk(ti) OR mortality(tiab) OR prognostic(tiab) OR marker(tiab)) AND (meta-anal*(tiab) OR systematic(sb) OR review(pt) OR random*(tiab) OR RCT(tiab) OR cohort studies(mh) OR cohort study(tiab) OR research support, non-U.S. Gov't(pt)) AND (hasabstract(text) AND ("2005/01/01"(PDat) : "3000/12/31"(PDat)) AND English(lang))) (minus eerste search) > 501	512

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Liu, 2016	Populatie betreft hypertensieve patiënten die een algemene operatie ondergaan; risico op acuut nierfalen
Van Lueder, 2015	Populatie: patiënten met MI; geen NCI berekend
Berezin, 2016	Associatie tussen comorbiditeiten en micropartikels
Bjornstad, 2014	Populatie: patiënten met diabetes mellitus type 1
Dutta, 2013	Betreft een populatie van 70 jaar of ouder
Kim, 2013	Populatie: patiënten met hartfalen en dyspneu
Ky, 2012	Populatie: patiënten met chronisch systolisch hartfalen
Levantesi, 2013	Toevoeging van urinezuurmetingen aan een niet reeds bestaande risicomodel
Abbasi, 2012	Predictie van diabetes mellitus type 2; externe validatie van een model
Chien, 2011	Predictiemodel voor hypertensie

Noot 10: Artritis psoriatica

Zoekverantwoording

Database	Zoektermen	Totaal
Medline (PubMed) 2005-aug 2017 Nederlands, Engels	(cardiovascular diseases(mj) OR CVD(tiab) OR cardiovascular(tiab) OR vascular disease(tiab) OR vascular event*(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk assessment(tiab) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tiab) OR incidence(tiab) OR prevalence(tiab)) AND (meta-anal*(tiab) OR systematic(sb) OR review(pt) OR cohort studies(mh) OR cohort study(tiab) OR case control(tiab) OR research support, non-U.S. Gov't(pt) OR relative risk(tiab) OR odds ratio(tiab)) AND (arthritis, psoriatic(mh) OR psoriatic arthritis(tiab)) (LH, NHG)	211

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Atzeni, 2011	Narratieve review
Castaneda, 2015	Onduidelijk of ook de incidentie van HVZ is onderzocht
Edson-Heredia, 2015	Niet vergeleken met de algemene populatie (vergeleken met milde/ernstige psoriatica)
Jamnitski, 2013	Systematische review (gezocht tot april 2011); geen Risk of Bias beoordeling; aantal studies geïncludeerd die in deze zoekactie zijn geëxcludeerd
Roifman, 2011	Recentere review beschikbaar; geen gedetailleerde zoekstrategie
Agca, 2016	Narratieve review
Han, 2006	Incidentie van HVZ niet onderzocht (vanwege te korte follow-up spreekt men van prevalentie)
Khraishi, 2014	Incidentie van HVZ niet gemeten
Ogdie, 2017	Check overlap met studie uit 2015; zelfde getallen, vanwege doel studie van 2015 meegenomen
Wibetoe, 2017	Verdeling van het risico op HVZ, niet zozeer de associatie tussen PA en incident HVZ
Polachek, 2017	Niet alleen cohortstudies geïncludeerd
Oh, 2017	Niet vergeleken met de algemene populatie
Gulati, 2016	Alleen het risico op HVZ berekend met SCORE; maar niet incidentie onderzocht
Eder, 2016	Niet vergeleken met de algemene populatie; voorspeller van HVZ binnen PSA-populatie
Vanaclocha, 2015	Incidentie van HVZ niet gemeten
Ernste, 2015	Uitkomst van interest niet gerapporteerd
Li, 2015	Niet gecorrigeerd voor confounding
Vanaclocha, 2014	Incidentie van HVZ niet gemeten
Favarato, 2014	Incidentie van HVZ niet gemeten
Miller, 2013	Associatie tussen psoriasis en HVZ; subgroep naar artritis gekeken, maar onduidelijk wat de vergelijking is; Risk of Bias beoordeling
Horreau, 2013	Associatie tussen psoriasis en HVZ; niet naar artritis gekeken
Arumugam, 2012	Narratieve review
Ahlehoff, 2011	Alleen psoriasispatiënten geïncludeerd, niet naar artritis gekeken
Tobin, 2010	Recentere review beschikbaar; geen gedetailleerde zoekstrategie
Buckley, 2010	Geen uitkomst van interesse
Gladman, 2009	Incidentie van HVZ niet gemeten
Kondratiouk, 2008	Incidentie van HVZ niet gemeten

Noot 11: COPD

Zoekverantwoording

Database	Zoektermen	Totaal
Medline (PubMed) 2005-april 2017 Engels, Nederlands	(cardiovascular diseases(mh) OR CVD(tiab) OR cardiovascular(tiab) OR vascular disease(tiab) OR vascular event*(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (meta-analysis(pt) OR meta-anal*(tiab) OR systematic(sb) OR systematic review(ti)) AND (pulmonary disease, chronic obstructive(mh) OR chronic obstructive pulmonary desease(tiab) OR COPD(tiab))	135

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Lusardi, 2008	Narratieve review
Morgan, 2010	Gepubliceerd voor meta-analyse

Mullerova, 2013	Narrative review
Rothnie, 2015	Onderzocht alleen de uitkomstaat het risico op een myocardinfarct

Noot 12: Jicht

Zoekverantwoording

Database	Zoektermen	Totaal
Medline (PubMed) 2005-feb 2017	(gout(mj) OR gout(tiab)) AND (cardiovascular diseases/epidemiology(mj) OR cardiovascular diseases/etiology(mj) OR cardiovascular diseases/mortality(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk(ti) OR mortality(tiab)) AND (meta-anal*(tiab) OR systematic(sb) OR review(pt) OR random*(tiab) OR RC(tiab) OR cohort studie((mh) OR cohort study(tiab) OR research support, non-U.S. Gov't(pt))	153

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Schieir, 2017	Uitkomst alleen MI
Kuo, 2016	HVZ niet als een composiet eindpunt genomen
Wiseman, 2016	Systematische review met 1 studie over jicht geïncludeerd: Seminog (e.a.) 2013 (reeds gevonden)
Abeles, 2015	Narratieve review
Liu, 2015	Uitkomst alleen MI
Van der Burg, 2015	Cohortstudie met 50% lost-to-follow-up en werkende patiënten
Bhole, 2014	Narratieve review
Karis, 2014	Narratieve review
Meek, 2014	Controls bestonden uit patiënten met andere reumatoïde aandoeningen i.p.v. jicht
Van Durme, 2014	Systematische review: breed ingestoken. Vanwege heterogeniteit geen meta-analyse; studies met een high Risk of Bias waren geëxcludeerd; geen evidence-tabellen beschikbaar
Perez-Ruiz, 2014	Review over mortaliteit ten gevolge van HVZ reeds geïncludeerd
Seminog, 2013	Uitkomst MI en beroerte apart
Stack, 2013	Niet iedereen was HVZ-vrij op baseline
Lottmann, 2012	Recentere review beschikbaar
Teng, 2012	Recentere review beschikbaar
Kuo, 2011	Zelfde populatie als Kuo, 2010; reeds geïncludeerd door Clarson, 2015b
Shah, 2010	Narratieve review (mogelijk gebruiken voor overwegingen)
De Vera, 2010	Geïncludeerd door Clarson, 2015b
Kuo, 2010	Geïncludeerd door Clarson, 2015b
Keenan, 2009	Narratieve review
Krishnan, 2008	Narratieve review
Krishnan, 2008	Reeds geïncludeerd door Clarson, 2015b
Kim, 2008	Recentere review beschikbaar
Choi, 2007	Geëxcludeerd door Clarson, 2015b (onzeker over geen CVD op baseline)
Baker, 2007	Associatie tussen urinezuur en PAD
Krishnan, 2006	Zelfde studie als Krishnan, 2008
Saag, 2005	Narratieve review
Luk, 2005	Narratieve review

Noot 13: Reumatoïde artritis

Zoekverantwoording

Systematische reviews/meta-analyse

Database	Zoektermen	Totaal
PubMed	(cardiovascular diseases(mh) OR CVD(tiab) OR cardiovascular(tiab) OR vascular disease(tiab) OR vascular event*(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (meta-analysis(pt) OR meta-anal*(tiab) OR systematic(sb) OR systematic review(ti)) AND (arthritis, rheumatoid(mh) OR reumatoid arthritis(tiab))	86

Observationeel onderzoek vanaf juni 2011

Database	Zoektermen	Totaal
PubMed	(cardiovascular diseases/etiology(mj) OR cardiovascular diseases/epidemiology(mj) OR CVD(tiab) OR cardiovascular(tiab) OR vascular disease(tiab) OR vascular event*(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (cohort studies(mh) OR cohort study(tiab) OR observational study(pt) OR observational(tiab) OR observation(mh)) AND (arthritis, rheumatoid(mh) OR reumatoid arthritis(tiab))	266

Exclusietabel observationele onderzoeken

Auteur en jaartal	Redenen van exclusie
Solomon, 2015	Nieuw risicomodel
Crowson, 2012	Nieuwe risicoscores
Khan, 2013	Geen vergelijkende groep
Meek, 2014	Geen vergelijkende groep
Van den Hoek, 2016	Geen vergelijkende groep
Jafri, 2017	Incidentie van CV-risicofactoren
Sparks, 2016	Alleen vrouwen, andere definitie van cardiovasculaire ziekten (incl. o.a. longembolie)
Masi, 2017	andere onderzoeksopzet
Dadoun, 2013	alleen totale mortaliteit

Noot 14: Ziekte van Bechterew

Zoekverantwoording

Database	Zoektermen	Totaal
PubMed 2005-juli 2017 Engels	(cardiovascular diseases(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR cardiovascular event(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tia)) OR incidence(tiab) OR prevalence(tiab)) AND (meta-anal*(tiab) OR systematic(sb) OR review(pt) OR cohort studies(mh) OR cohort study(tiab) OR research support, non-U.S. Gov't(pt)) AND (spondylitis, ankylosing(mh) OR ankylosing spondylitis(tiab) OR Bechterew*(tiab) OR Bechterew's(tiab) OR ankylosing spondylarthritis(tiab) OR akylosing spondyloarthritis(tiab)) – LH/NHG	124

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Agca, 2017	PICO heel breed, consensus based. Wel gebruiken voor overwegingen
Wright, 2015	Cumulatieve 10-jaars incidentie CVD berekend, geen risicoschatting
Roifman, 2011	O: coronary artery disease
Han, 2006	Prevalence ratio's only for comorbidities, not for total CVD

Noot 15: Hiv

Zoekverantwoording

Database	Zoektermen	Totaal
Medline (PubMed) 2005-mei 2017 Engels, Nederlands	(cardiovascular diseases(mh) OR CVD(tiab) OR cardiovascular(tiab) OR vascular disease(tiab) OR vascular event*(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (meta-analysis(pt) OR meta-anal*(tiab) OR systematic(sb) OR systematic review(ti)) AND (HIV(mh) OR HIV infections(mh) OR HIV*(tiab) OR human immunodeficiency virus*(tiab))	99
Medline (PubMed) 2010-sep 2017 Engels, Nederlands	(cardiovascular diseases/etiology(mj) OR CVD(tiab) OR cardiovascular(tiab) OR vascular disease(tiab) OR vascular event*(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND (predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tiab) OR incidence(ti) OR prevalence(ti)) AND (randomized controlled trial(pt) OR randoml*(tiab) OR RCT(tiab) OR cohort studies(mh) OR cohort study(tiab)) AND (HIV(mh) OR HIV infections(mh) OR HIV*(tiab) OR human immunodeficiency virus*(tiab))	525

Exclusietabel

Exclusiereden	Auteur
Exclusie, alleen het risico per hart- en vaatziekte bij gebruik anti-retrovriale medicatie, geen totaal risico op HVZ	C. Bavinger, E. Bendavid, K. Niehaus, R. A. Olshen, I. Olkin, V. Sundaram, N. Wein, M. Holodniy, N. Hou, D. K. Owens and M. Desai. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. PLoS One 2013;8:e59551.
Exclusie, narratieve review	D. Chow, C. Shikuma, C. Ritchings, M. Guo, L. Rosenblatt. Atazanavir and Cardiovascular Risk Among Human Immunodeficiency Virus-Infected Patients: A Systematic Review. Infect Dis Ther 2016;5:473-489.
Exclusie, alleen gericht op abacavir	M. Cruciani, V. Zanichelli, G. Serpelloni, O. Bosco, M. Malena, R. Mazzi, C. Mengoli, S.G. Parisi and G. Moyle. Abacavir use and cardiovascular disease events: a meta-analysis of published and unpublished data. Aids 2011;25:1993-2004.
Exclusie, alleen gericht op abacavir	X. Ding, E. Andraca-Carrera, C. Cooper, P. Miele, C. Kornegay, M. Soukup and K.A. Marcus. No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis. J Acquir Immune Defic Syndr 2012;61:441-7.
Exlsuise, geeft geen risico op HVZ	M. Farahani, H. Mulinder, A. Farahani and R. Marlink. Prevalence and distribution of non-AIDS causes of death among HIV-infected individuals receiving antiretroviral therapy: a systematic review and meta-analysis. Int J STD AIDS 2017;28:636-650.
Inclusie	F.M. Islam, J. Wu, J. Jansson and D.P. Wilson. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. HIV Med 2012;13:453-68.
Exclusie, narratieve review	J.M. Llibre and A. Hill. Abacavir and cardiovascular disease: A critical look at the data. Antiviral Res 2016;132:116-21.
Exclusie, narratieve review	M.J. Siedner. START or SMART? Timing of Antiretroviral Therapy Initiation and Cardiovascular Risk for People With Human Immunodeficiency Virus Infection. Open Forum Infect Dis 2016;3:ofw032.

Noot 16: IBD

Zoekverantwoording

Database	Zoektermen	Totaal
Medline (PubMed)	(cardiovascular diseases(mj) OR CVD(tiab) OR cardiovascular disease(tiab) OR vascular disease(tiab) OR vascular event(tiab) OR coronary heart disease(tiab) OR CHD(tiab)) AND	327

2005-april 2017 Engels, Nederlands	(predict*(tiab) OR statistics as topic(mh) OR risk assessment(mh) OR risk factors(mh) OR increased risk(tiab) OR risk score(tiab) OR risk(ti) OR mortality(tiab) OR incidence(tiab) OR prevalence(tiab)) AND (meta-anal*(tiab) OR systematic(sb) OR review(pt) OR random*(tiab) OR RCT(tiab) OR cohort studies(mh) OR cohort study(tiab) OR research support, non-U.S. Gov't(pt)) AND (inflammatory bowel diseases(mh) OR crohn disease(mh) OR colitis, ulcerative(mh) OR inflammatory bowel disease(tiab) OR IBD(tiab) OR crohn disease(tiab) OR crohn's disease(tiab) OR ulcerative colitis(tiab))	

In- en exclusietabel

In- of exclusie en reden	
Exclusie; wel syst. gezocht, maar daarna uitsluitend narratief zonder beschreven methodologie	C. Rungoe and N. Nyboe Andersen and T. Jess,. Inflammatory bowel disease and risk of coronary heart disease. Trends Cardiovasc Med 2015;25:699-704.
Exclusie, verkeerde populatie (met CAD)	A. Aggarwal and A. Atreja and S. Kapadia and R. Lopez and J. P. Achkar. Conventional risk factors and cardiovascular outcomes of patients with inflammatory bowel disease with confirmed coronary artery disease. Inflamm Bowel Dis 2015;21:E2.
Exclusie; narratief	N.N. Andersen and T. Jess. Risk of cardiovascular disease in inflammatory bowel disease. World J Gastrointest Pathophysiol 2014;5:359-65.
Exclusie; VOOR 1 maart 2013 van SR/MA Singh	F. Andersohn and M. Waring and E. Garbe. Risk of ischemic stroke in patients with Crohn's disease: a population-based nested case-control study. Inflamm Bowel Dis 2010;16:1387-92.
Exclusie; VOOR 1 maart 2013 van SR/MA Singh	C.N. Bernstein and A. Wajda and J. F. Blanchard. The incidence of arterial thromboembolic diseases in inflammatory bowel disease: a population-based study. Clin Gastroenterol Hepatol 2008;6:41-5.
Inclusie; SR naar all-cause en cause specific mortality	M. Bewtra and L. M. Kaiser and T. TenHave and J. D. Lewis. Crohn's disease and ulcerative colitis are associated with elevated standardized mortality ratios: a meta-analysis. Inflamm Bowel Dis 2013;19:599-613.
Inclusie, aanvullend op SR/MA Singh	H. Close and J.M. Mason and D.W. Wilson and A.P. Hungin and R. Jones and G. Rubin. Risk of Ischaemic Heart Disease in Patients with Inflammatory Bowel Disease: Cohort Study Using the General Practice Research Database. PLoS One 2015;10:e0139745.
Inclusie; SR naar CV specific mortality	S.D. Dorn and R.S. Sandler. Inflammatory bowel disease is not a risk factor for cardiovascular disease mortality: results from a systematic review and meta-analysis. Am J Gastroenterol 2007;102:662-7.
Inclusie; cohort 2014; eindpunten DM2/stroke/CHD	A. Dregan and J. Charlton and P. Chowienczyk and M. C. Gulliford. Chronic inflammatory disorders and risk of type 2 diabetes mellitus, coronary heart disease, and stroke: a population-based cohort study. Circulation 2014;130(10):837-44.
Exclusie; eindpunt is risk factor assessment	G. Emanuel and J. Charlton and M. Ashworth and M. C. Gulliford and A. Dregan. Cardiovascular risk assessment and treatment in chronic inflammatory disorders in primary care. Heart 2016;102:1957-1962.
Exclusie; narratief	A.M. Filimon and L. Negreanu and M. Doca and A. Ciobanu and C. M. Preda and D. Vinereanu. Cardiovascular involvement in inflammatory bowel disease: Dangerous liaisons. World J Gastroenterol 2015;21:9688-92.
Inclusie; zoekdatum tot juni 2012	M. Fumery and C. Xiaocang and L. Dauchet and C. Gower-Rousseau and L. Peyrin-Biroulet and J.F. Colombel. Thromboembolic events and cardiovascular mortality in inflammatory bowel diseases: a meta-analysis of observational studies. J Crohns Colitis 2014;8:469-79.
Exclusie; wel syst. gezocht, maar daarna uitsluitend narratief zonder beschreven methodologie	S. Gandhi and N. Narula and J.K. Marshall and M. Farkouh. Are patients with inflammatory bowel disease at increased risk of coronary artery disease? Am J Med 2012;125:956-62.

Exclusie; VOOR 1 maart 2013 van SR/MA Singh	C. Ha and S. Magowan and N.A. Accortt and J. Chen and C.D. Stone. Risk of arterial thrombotic events in inflammatory bowel disease. Am J Gastroenterol 2009;104:1445-51.
Exclusie; VOOR 1 maart 2013 van SR/MA Singh	J. Haapamaki and R.P. Roine and U. Turunen and M.A. Farkkila and P.E. Arkkila. Increased risk for coronary heart disease, asthma, and connective tissue diseases in inflammatory bowel disease. J Crohns Colitis 2011;5:41-7.
Inclusie; eindpunt stroke voor cohort IBD 2014	W.S. Huang and C. H. Tseng and P.C. Chen and C.H. Tsai and C.L. Lin and F.C. Sung and C.H. Kao. Inflammatory bowel diseases increase future ischemic stroke risk: a Taiwanese population-based retrospective cohort study. Eur J Intern Med 2014;25:561-5.
Exclusie; gaat over IBS/obstipatie, niet IBD!	C. Huerta and E. Rivero and M.A. Montoro and L.A. Garcia-Rodriguez. Risk factors for intestinal ischaemia among patients registered in a UK primary care database: a nested case-control study. Aliment Pharmacol Ther 2011;33:969-78.
Inclusie, aanvullend op SR/MA Singh	A. Jussila and L.J. Virta and E. Pukkala and M.A. Farkkila. Mortality and causes of death in patients with inflammatory bowel disease: a nationwide register study in Finland. J Crohns Colitis 2014;8:1088-96.
Inclusie; eindpunt stroke voor cohort CU 2014	J.J. Keller and J. Wang and Y.L. Huang and C.C. Chou and L.H. Wang and J.L. Hsu and C.H. Bai and H.Y. Chiou. Increased risk of stroke among patients with ulcerative colitis: a population-based matched cohort study. Int J Colorectal Dis 2014;29:805-12.
Inclusie; eindpunt stroke voor cohort Crohn 2014	J.J. Keller and J. Wang and Y.L. Hwang and C.C. Chou and L.H. Wang and J.L. Hsu and C.H. Bai and H.Y. Chiou. Increased risk of stroke among patients with Crohn's disease: a population-based matched cohort study. Int J Colorectal Dis 2015;30:645-53.
Exclusie; VOOR 1 maart 2013 van SR/MA Singh	S.L. Kristensen and O. Ahlehoff and J. Lindhardsen and R. Erichsen and G.V. Jensen and C. Torp-Pedersen and O.H. Nielsen and G.H. Gislason and P.R. Hansen. Disease activity in inflammatory bowel disease is associated with increased risk of myocardial infarction, stroke and cardiovascular death--a Danish nationwide cohort study. PLoS One 2013;8:e56944.
Exclusie: eindpunt heart failure	S.L. Kristensen and O. Ahlehoff and J. Lindhardsen and R. Erichsen and M. Lamberts and U. Khalid and O.H. Nielsen and C. Torp-Pedersen and G.H. Gislason and P.R. Hansen. Inflammatory bowel disease is associated with an increased risk of hospitalization for heart failure: a Danish Nationwide Cohort study. Circ Heart Fail. 2014;7:717-22.
Inclusie; eindpunt AF en stroke voor cohort IBD 2013	L. Kristensen and J. Lindhardsen and O. Ahlehoff and R. Erichsen and M. Lamberts and U. Khalid and C. Torp-Pedersen and O.H. Nielsen and G.H. Gislason and P.R. Hansen. Increased risk of atrial fibrillation and stroke during active stages of inflammatory bowel disease: a nationwide study. Europace 2014;16:477-84.
Exclusie; gaat over trend in incidentie in 10-jaar	S. Kuy and A. Dua and R. Chappidi and G. Seabrook and K.R. Brown and B. Lewis and P.J. Rossi and C.J. Lee. The increasing incidence of thromboembolic events among hospitalized patients with inflammatory bowel disease. Vascular 2015;23:260-4.
Exclusie; narratief	O. Mitu and D.M. Alexandrescu and M. Catalina and C.P. Cristina. Is there a cardiovascular risk in inflammatory bowel diseases? Rev Med Chir Soc Med Nat Iasi 2014;118:918-23.
Exclusie; VOOR 1 maart 2013 van SR/MA Singh	M.T. Osterman and Y.X. Yang and C. Brensinger and K.A. Forde and G.R. Lichtenstein and J.D. Lewis. No increased risk of myocardial infarction among patients with ulcerative colitis or Crohn's disease. Clin Gastroenterol Hepatol 2011;9:875-80.
Exclusie; VOOR 1 maart 2013 van SR/MA Singh	C. Rungoe and S. Basit and M.F. Ranthe and J. Wohlfahrt and E. Langholz and T. Jess. Risk of ischaemic heart disease in patients with inflammatory bowel disease: a nationwide Danish cohort study. Gut 2013;62:689-94.
Exclusie; narratief	R. Schicho and G. Marsche and M. Storr. Cardiovascular complications in inflammatory bowel disease. Curr Drug Targets 2015;16:181-8.

Exclusie; narratief	S. Singh and I.J. Kullo and D.S. Pardi and Jr. Loftus, E.V. Epidemiology, risk factors and management of cardiovascular diseases in IBD. Nat Rev Gastroenterol Hepatol 2015;12:26-35.
Inclusie; zoekdatum tot 1 maart 2013 --> golden hit	S. Singh and H. Singh and Jr. Loftus, E.V. and D.S. Pardi. Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014;12:382-93.e1: quiz e22.
Inclusie; Tabel 2!	V.P. Tan and A. Chung and B.P. Yan and P.R. Gibson. Venous and arterial disease in inflammatory bowel disease. J Gastroenterol Hepatol 2013;28:1095-113.
Exclusie: composite eindpunt inclusief heart failure	S.D. Thapa and H. Hadid and J. Schairer and W. Imam and S.M. Jafri. Effect of Inflammatory Bowel Disease-Related Characteristics and Treatment Interventions on Cardiovascular Disease Incidence. Am J Med Sci 2015;350:175-80.
Inclusie, aanvullend op SR/MA Singh; eindpunt ACS	M.S. Tsai and C.L. Lin and H.P. Chen and P.H. Lee and F.C. Sung and C.H. Kao. Long-term risk of acute coronary syndrome in patients with inflammatory bowel disease: a 13-year nationwide cohort study in an Asian population. Inflamm Bowel Dis 2014;20:502-7.
Inclusie; alleen uitkomst stroke; zoekdatum tot 1 juni 2015	Z. Xiao and Z. Pei and M. Yuan and X. Li and S. Chen and L. Xu. Risk of Stroke in Patients with Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. J Stroke Cerebrovasc Dis 2015;24:2774-80.
Exclusie; VOOR 1 maart 2013 van SR/MA Singh	A.J. Yarur and A.R. Deshpande and D.M. Pechman and L. Tamariz and M.T. Abreu and D.A. Sussman. Inflammatory bowel disease is associated with an increased incidence of cardiovascular events. Am J Gastroenterol 2011;106:741-7.
Exclusie; VOOR 1 maart 2013 van SR/MA Singh	B. Zoller and X. Li and J. Sundquist and K. Sundquist. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. BMC Neurol 2012;12:41.
Exclusie; cross-sectionele studie	F. Aguero and G. Gonzalez-Zobl and J.M. Baena-Diez and I.R. Degano and M. Garcia-Gil and M.T. Alzamora and J. Marrugat and M. Comas-Cufi and G. Pera and R. Elosua and R. Ramos and M. Grau. Prevalence of lower extremity peripheral arterial disease in individuals with chronic immune mediated inflammatory disorders. Atherosclerosis 2015;242:1-7.
Exclusie; narratief	D. Kohoutova and P. Moravkova and P. Kruzliak and J. Bures. Thromboembolic complications in inflammatory bowel disease. J Thromb Thrombolysis 2015;39:489-98.
Inclusie, aanvullend op SR/MA Singh; eindpunt PAD	T.Y. Lin and Y.G. Chen and C.L. Lin and W.S. Huang and C.H. Kao. Inflammatory Bowel Disease Increases the Risk of Peripheral Arterial Disease: A Nationwide Cohort Study. Medicine (Baltimore) 2015;94:e2381.
Inclusie; gaat over div. inflamm. ziekten; zoekdatum juni 2010	I. Roifman and P.L. Beck and T.J. Anderson and M.J. Eisenberg and J. Genest. Chronic inflammatory diseases and cardiovascular risk: a systematic review. Can J Cardiol 2011;27:174-82.
Inclusie, aanvullend op SR/MA Singh; eindpunt mesenteriaal ischaemie	M.S. Tsai and C.L. Lin and H.P. Chen and P.H. Lee and F.C. Sung and C.H. Kao. Long-term risk of mesenteric ischemia in patients with inflammatory bowel disease: a 13-year nationwide cohort study in an Asian population. Am J Surg 2015;210:80-6.
Exclusie; narratief	P. Zezos and G. Kouklakis and F. Saibil. Inflammatory bowel disease and thromboembolism. World J Gastroenterol 2014;20:13863-78.

Noot 23: Leefstijladviezen bij kwetsbare ouderen

Zoekverantwoording

Database	Zoektermen	Totaal
Medline (OVID) 1980-juni 2016 Engels, Nederlands, Duits	1 Cardiovascular Diseases/pc (Prevention & Control) (27444) 2 exp Heart Diseases/pc (Prevention & Control) (63611) 3 exp Vascular Diseases/pc (Prevention & Control) (117823) 4 (cardiovascular or heart*).ti. (367954) 5 1 or 2 or 3 or 4 (506200) 6 exp Aged/ or aged.ti. or exp Frail Elderly/ or "Aged, 80 and over"/ or exp Aging/ or exp Geriatric Assessment/ or (elderly or geriatric or 'community dwelling' or frail* or ag?ing or septuagenarian or octogenarian or nonagenarian or centenarian or 'old people' or eldest or oldest).ti,ab. or (individual adj2 (patient* or participant*) adj1 data*).ti,ab. (2873749) 7 5 and 6 (104476) 8 exp *"Tobacco Use Cessation"/ (16980) 9 *Weight Loss/ (12336) 10 (Weight adj3 (loss or reduction)).ti,ab. (77528) 11 (smoking adj3 (cess* or stopp* or quit*)).ti,ab. (24350) 12 8 or 9 or 10 or 11 (109146) 13 7 and 12 (1257) 14 limit 13 to (yr="1980 -Current" and (dutch or english or german)) (1173) 15 12 and 14 (1173) 16 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (276516) 17 15 and 16 (48) – 46 uniek 18 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1558455) 19 15 and 18 (503) 20 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies) (2590118) 21 15 and 20 (555) 2 17 or 19 (517) 23 21 not 22 (328) 24 22 or 23 (845) 25 19 or 21 (839) 26 25 not 17 (797) 27 remove duplicates from 26 (769)	815

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Review filter	
Hartley, 2014	Niet gericht op gewichtsreductie
Aucott, 2009	Studies included with age at recruitment between 18 and 65 years
RCT-filter	
Waters, 2013	Gezocht in 1 database en geen zoekstrategie beschikbaar
Espeland, 2013	Gericht op patiënten met diabetes in de leeftijd tussen 65 en 76 jaar
Oerkild, 2012	Lichamelijke oefeningen gericht op revalidatie
Pascual, 2011	Studieprotocol; check voor publicatie (niet gevonden)
Arnold, 2010	Betreft veranderingen in gewicht en het effect op mortaliteit. Veranderingen in gewicht niet door een interventie

Richard, 2009 Moll van Charante, 2016*	Betreft risicofactoren voor hart- en vaatziekten Individueel afgestemde interventie. Resultaten niet per onderdeel weergegeven
Clark, 2009	Algemene interventie; niet in het bijzonder gericht op het stoppen met roken of gewichtsreductie
Andersson, 2009	Beschrijving van de lead-periode van een RCT; voor-na vergelijkingen
Pischke, 2008	Deelnemers waren gemiddeld jonger dan 70 jaar
Perreault, 2008	Deelnemers waren gemiddeld jonger dan 70 jaar; deelnemers met een verhoogde kans op diabetes
Katcher, 2008	Deelnemers waren gemiddeld jonger dan 70 jaar
Joseph, 2008	Deelnemers waren gemiddeld jonger dan 70 jaar
Reid, 2007	Deelnemers waren gemiddeld jonger dan 70 jaar
Mohiuddin, 2007	Deelnemers waren gemiddeld jonger dan 70 jaar
Keogh, 2007	Deelnemers waren gemiddeld jonger dan 70 jaar
Burke, 2007	Deelnemers waren gemiddeld jonger dan 70 jaar
Kuller, 2006	Deelnemers waren gemiddeld jonger dan 70 jaar
Zwisler, 2005	Deelnemers waren gemiddeld jonger dan 70 jaar
Hatsukami, 2005	Deelnemers waren gemiddeld jonger dan 70 jaar
De Simone, 2005	Deelnemers waren gemiddeld jonger dan 70 jaar
Sivarajan Froelicher, 2004	Deelnemers waren gemiddeld jonger dan 70 jaar
Fleming, 2002	Deelnemers waren gemiddeld jonger dan 70 jaar
McCarron, 2001	Deelnemers waren gemiddeld jonger dan 70 jaar
Metz, 2000	Deelnemers waren gemiddeld jonger dan 70 jaar
Simkin-Silverman, 1998	Interventie gericht op leefstijladviezen, niet op het stoppen met roken of gewichtsreductie
Ornish, 1999	Deelnemers waren gemiddeld jonger dan 70 jaar
McCarron, 1997	Vergelijking tussen twee verschillende diëten
Suurkala, 1996	Deelnemers waren gemiddeld jonger dan 70 jaar; interventie niet alleen gericht op het stoppen met roken of gewichtsreductie

* Een recentere publicatie van dezelfde studie is ook bekeken. Beide publicaties voldeden niet aan de inclusiecriteria.

Noot 25: Streefwaarden van LDL-C

Zoekverantwoording

Database	Zoektermen		Totaal
Medline (OVID) 2005-juni 2017 Engels, Nederlands	1	exp *Cardiovascular Diseases/ or (cardiovascular disease* or CVD or vascular disease* or vascular event* or coronary heart disease or CHD).ti,ab,kf. (1961435)	828
	6	*Cholesterol, LDL/ or ((LDL or low-density lipoprotein) adj3 (C or cholesterol)).ti,ab,kf. (53396)	
	7	(preventi* or statin* or control or therapy).ti,ab,kf. (4244147)	
	8	(dt or tu or pc).fs. (3562424)	
	9	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (35783)	
	10	(hmg coa reductase inhibitor* or statin* or Atorvastatin* or Lovastatin* or Meglutol* or Pravastatin* or Rosuvastatin* or Simvastatin*).ti,ab,kf. (49677)	
	11	Reference Values/ or target*.ti,ab,kf. or risk.ti. or mortality.ti,ab. or incidence.ti. or relation*.ti. or association.ti. or lipid-modifying.ti. or lipid level*.ti,ab. or reduction.ti,ab. or lowering.ti,ab. (3613106)	
	12	7 or 8 or 9 or 10 or 11 (8796660)	
	13	1 and 6 and 12 (20559)	
	14	limit 13 to (yr="2005 -Current" and (dutch or english)) (12440)	
	15	(meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (331922)	
	16	14 and 15 (702)	

	17 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or clinic$ trial$1.tw. or (clinic$ adj trial$1).tw. or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo$.tw. or randomly allocated.tw. or (allocated adj2 random$).tw.) not (animals/ not humans/) (1372576) 18 14 and 17 (4183) 21 18 not 16 (3791) 26 remove duplicates from 16 (643) – 638 uniek	
Embase (Elsevier)	'low density lipoprotein cholesterol'/exp/mj OR 'very low density lipoprotein cholesterol'/exp/mj OR ((ldl OR 'low-density lipoprotein*') NEAR/3 (c OR cholesterol)):ti,ab AND ('cardiovascular disease'/exp/mj OR 'cardiovascular disease*':ti,ab OR cvd:ti,ab OR 'vascular disease*':ti,ab OR 'vascular event*':ti,ab OR 'coronary heart disease':ti,ab OR chd:ti,ab) AND (preventi*:ti,ab OR control:ti,ab OR therapy:ti,ab OR 'drug therapy':lnk OR prevention:lnk OR 'hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp/mj OR 'hmg coa reductase inhibitor*':ti,ab OR statin*:ti,ab OR atorvastatin*:ti,ab OR lovastatin*:ti,ab OR meglutol*:ti,ab OR pravastatin*:ti,ab OR rosuvastatin*:ti,ab OR simvastatin*:ti,ab OR target*:ti,ab OR risk:ti OR mortality:ti,ab OR incidence:ti OR relation*:ti OR association:ti OR 'lipid modifying':ti OR 'lipid level*':ti,ab OR reduction:ti,ab OR lowering:ti,ab OR 'reference value'/exp) AND ((dutch)/lim OR (english)/lim) AND (embase)/lim AND (2005-2017)/py NOT 'conference abstract':it AND ('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp) (622) – 190 uniek	

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Soran, 2017	Gezocht in 1 database; zoekstrategie niet beschikbaar
Olsson, 2017	Narratieve review
Bahiru, 2017	Niet alleen cholesterolverlagende medicatie; vergeleken met placebo
Lafeber, 2017	RCT polypill versus usual care
Schmidt, 2017	Systematische review naar effectiviteit van PCSK9-antilichamen
Jena, 2016	Data uit een cohortstudie
Peng, 2016	Geen Risk of Bias beoordeling per studie (wel voor publicatiebias)
Webster, 2016	Geen systematische zoekactie
Cai, 2015	Associatie tussen genetische afwijking en HVZ
Cholesterol Treatment Trialists, 2015	Geen systematische zoekactie
Karlson, 2015	Geen systematische zoekactie; gesponsord door farmaceut
Preiss, 2015	RCT's vergeleken met placebo geïncludeerd
Thomopoulos, 2015	RCT's vergeleken met placebo geïncludeerd
Boekholdt, 2014	Gezocht in 1 database
Bruckert, 2014	Narratieve review
Gudzune, 2014	Systematische review van intensieve behandeling met lipidenverlagende medicatie versus minder intensief
Naci, 2014	Effectschatters niet gerapporteerd omdat het doel van review het onderzoeken van industry-sponsored bias was
Soran, 2014	Narratieve review
Karlson, 2013	Geen systematische zoekactie; gesponsord door farmaceut
Naci, 2013	Effectschatters niet gerapporteerd omdat het doel van review het onderzoeken van industry-sponsored bias was
Ribeiro, 2013	Geen uitkomst LDL-waarde
Ye, 2012	Uitkomst van interesse endotheelfunctie

Morrone, 2012	Niet systematisch gezocht
Cholesterol Treatment Trialists, 2012	Geen systematische zoekactie
McKinney, 2012	RCT's vergeleken met placebo geïncludeerd
Sniderman, 2011	Verschil tussen markers LDL, non-HDL en apoB
Chan, 2011	Systematische review van intensieve behandeling met statines versus minder intensief
Ramjee, 2011	Niet origineel; beschrijving van de CTT meta-analyse
Seehusen, 2011	Case report met review van literatuur

Noot 26: NON-HDL-cholesterol

Zoekverantwoording

Database	Zoektermen	Totaal
Medline (OVID) 2005-mei 2017 Engels, Nederlands	1 exp *Cardiovascular Diseases/ or (cardiovascular disease* or CVD or vascular disease* or vascular event* or coronary heart disease or CHD):ti,ab (1945995) 2 (Meta-analysis of the relationship between non-high-density lipoprotein cholesterol 6 ("non-HDL cholesterol" or "non-HDL C" or "non-high density" or "nonhigh-density"):ti,ab (2759) 7 *Cholesterol, HDL/ (6512) 8 *"Cholesterol"/bl (Blood) (17998) 9 6 or 7 or 8 (26208) 10 (preventi* or statin* or control or therapy):ti,ab (4204637) 11 (dt or tu or pc).fs. (3537667) 12 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (35366) 13 (hmg coa reductase inhibitor* or statin* or Atorvastatin* or Lovastatin* or Meglutol* or Pravastatin* or Rosuvastatin* or Simvastatin*):ti,ab (49036) 14 Reference Values/ or target*:ti,ab or risk.ti. or mortality:ti,ab. or incidence.ti. or relation*.ti. or association.ti. or lipid-modifying.ti. or lipid level*:ti,ab. or target*.ti. or reduction:ti,ab. or lowering:ti,ab. (3572844) 15 10 or 11 or 12 or 13 or 14 (8719776) 16 1 and 9 and 15 (6754) 17 limit 16 to (yr="2005 -Current" and (dutch or english)) (3166) 18 remove duplicates from 17 (3004) 19 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (326312) 20 18 and 19 (165) – 164 uniek	241
Embase (Elsevier)	'cardiovascular disease'/exp/mj OR 'cardiovascular disease*':ti,ab OR cvd:ti,ab OR 'vascular disease*':ti,ab OR 'vascular event*':ti,ab OR 'coronary heart disease':ti,ab OR chd:ti,ab AND ('non-hdl cholesterol':ti,ab OR 'non-hdl c':ti,ab OR 'non-high density':ti,ab OR 'nonhigh-density':ti,ab OR 'high density lipoprotein cholesterol'/exp/mj) AND (preventi*:ti,ab OR control:ti,ab OR therapy:ti,ab OR 'drug therapy':lnk OR prevention:lnk OR 'hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp/mj OR 'hmg coa reductase inhibitor*':ti,ab OR statin*:ti,ab OR atorvastatin*:ti,ab OR lovastatin*:ti,ab OR meglutol*:ti,ab OR pravastatin*:ti,ab OR rosuvastatin*:ti,ab OR simvastatin*:ti,ab OR (target*:ti,ab OR risk:ti OR mortality:ti,ab OR incidence:ti OR relation*:ti OR association:ti OR 'lipid modifying':ti OR “lipid level*”:ti,ab) OR reduction:ti,ab OR lowering:ti,ab OR 'reference value'/exp) AND ((dutch)/lim OR (english)/lim) AND (embase)/lim AND (2005-2017)/py AND ('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp)”(149)> 77 uniek MW-Kennisinstituut/LH-NHG	

Exclusietabel

Inclusie - of exclusiereden	Artikel
Exclusie, cohort, geen meta-analyse	Barzi, F. and Patel, A. and Woodward, M. and Lawes, C. M. and Ohkubo, T. and Gu, D. and Lam, T. H. and Ueshima, H. and Asia Pacific Cohort Studies, Collaboration. A comparison of lipid variables as predictors of cardiovascular disease in the Asia Pacific region. Ann Epidemiol 2005;15:405-13.
Inclusie	Boekholdt, S. M. and Arsenault, B. J. and Mora, S. and Pedersen, T. R. and LaRosa, J. C. and Nestel, P. J. and Simes, R. J. and Durrington, P. and Hitman, G. A. and Welch, K. M. and DeMicco, D. A. and Zwinderman, A. H. and Clearfield, M. B. and Downs, J. R. and Tonkin, A. M. and Colhoun, H. M. and Gotto, A. M., Jr. and Ridker, P. M. and Kastelein, J. "Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. JAMA 2012;307:1302-1309.
Exclusie, niet zoekvraag	Boekholdt, S.M. and Hovingh, G.K. and Mora, S. and Arsenault, B.J. and Amarenco, P. and Pedersen, T.R. and LaRosa, J.C. and Waters, D.D. and DeMicco, D.A. and Simes, R.J. and Keech, A.C. and Colquhoun, D. and Hitman, G.A. and Betteridge, D.J. and Clearfield, M.B. and Downs, J.R. and Colhoun, H.M. and Gotto, A.M., Jr. and Ridker, P.M. and Grundy, S.M. and Kastelein, J.J.Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol 2014;64:485-94.
	Cziraky, M.J. and Watson, K.E. and Talbert, R.L. Targeting low HDL-cholesterol to decrease residual cardiovascular risk in the managed care setting. J Manag Care Pharm 2008;14:S3-28; quiz S30-1.
Inclusie, maar meer recente meta-analyse	Emerging Risk Factors Collaboration and Di Angelantonio, E. and Sarwar, N. and Perry, P. and Kaptoge, S. and Ray, K.K. and Thompson, A. and Wood, A. M. and Lewington, S. and Sattar, N. and Packard, C.J. and Collins, R. and Thompson, S.G. and Danesh. Major lipids, apolipoproteins, and risk of vascular disease. JAMA 2009;302:1993-2000.
Exclusie, niet zoekvraag	Karlson, B.W. and Palmer, M.K. and Nicholls, S.J. and Lundman, P. and Barter, P.J. Doses of rosuvastatin, atorvastatin and simvastatin that induce equal reductions in LDL-C and non-HDL-C: Results from the VOYAGER meta-analysis. Eur J Prev Cardiol 2016;23:744-7.
Exclusie, niet zoekvraag	Kuhnast, S. and Fiocco, M. and Van der Hoorn, J.W. and Princen, H.M. and Jukema, J.W. Innovative pharmaceutical interventions in cardiovascular disease: Focusing on the contribution of non-HDL-C/LDL-C-lowering versus HDL-C-raising: A systematic review and meta-analysis of relevant preclinical studies and clinical trials. Eur J Pharmacol 2015;763:48-63.
Exclusie, niet zoekvraag	Liu, H. and Deng, X. and Peng, Y. and Zeng, Q. and Song, Z. and He, W. and Zhang, L. and Gao, G. and Xiao, T. and Yu. Meta-analysis of serum non-high-density lipoprotein cholesterol and risk of coronary heart disease in the general population. Clin Chim Acta 2017;471:23-28.
Exclusie, narratieve review	Rana, J.S. and Boekholdt, S.M. Should we change our lipid management strategies to focus on non-high-density lipoprotein cholesterol? Curr Opin Cardiol. 2010;25:622-6.
Exclusie, narratieve review	Rana, J.S. and Boekholdt, S.M. and Kastelein, J.J. and Shah, P.K. The role of non-HDL cholesterol in risk stratification for coronary artery disease. Curr Atheroscler Rep 2012;14:130-4.
Exclusie, niet zoekvraag	Robinson, J.G. and Wang, S. and Jacobson, T.A. Meta-analysis of comparison of effectiveness of lowering apolipoprotein B versus low-density lipoprotein cholesterol and nonhigh-density lipoprotein cholesterol for cardiovascular risk reduction in randomized trials. Am J Cardiol 2012;110:1468-76.
Inclusie, maar meer recente meta-analyse	Robinson, J.G. and Wang, S. and Smith, B.J. and Jacobson. Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. J Am Coll Cardiol 2009;53:316-22.

Exclusie, niet zoekvraag	Sandhu, P.K. and Musaad, S.M. and Remaley, A.T. and Buehler, S.S. and Strider, S. and Derzon, J.H. and Vesper, H. W. and Ranne, A. and Shaw, C.S. and Christenson, R. Lipoprotein Biomarkers and Risk of Cardiovascular Disease: A Laboratory Medicine Best Practices (LMBP) Systematic Review. J Appl Lab Med 2016;1:214-229.
Exclusie, narrative review	Sniderman, A. and McQueen, M. and Contois, J. and Williams, K. and Furberg, C.D. Why is non - High-density lipoprotein cholesterol a better marker of the risk of vascular disease than low-density lipoprotein cholesterol? J Clin Lipidol 2010;4:152-5.
Inclusie, maar meer recente meta-analyse	Sniderman, A.D. and Williams, K. and Contois, J.H. and Monroe, H.M. and McQueen, M.J. and De Graaf, J. and Furberg, C. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk" Circulation. Circ Cardiovasc Qual Outcomes 2011;4:337-45.
Exclusie, narrative review	Sniderman, A.D. and Williams, K. and McQueen, M.J. and Furberg, C.D. When is equal not equal? J Clin Lipidol 2010;4:83-8.
Exclusie, niet zoekvraag	Soran, H. and Kwok, S. and Adam, S. and Ho, J.H. and Durrington, P. Evidence for more intensive cholesterol lowering. Curr Opin Lipidol 2017;28:291-299.
Exclusie, niet zoekvraag	Thanassoulis, G. and Williams, K. and Ye, K. and Brook, R. and Couture, P. and Lawler, P.R. and De Graaf, J. and Furberg, C.D. and Sniderman. Relations of change in plasma levels of LDL-C, non-HDL-C and apoB with risk reduction from statin therapy: a meta-analysis of randomized trials. J Am Heart Assoc 2014;3:e000759.
Exclusie, niet zoekvraag	Toth, P. and Doyle, C. and Henriksson, K. Lack of improvement in non-high-density lipoprotein cholesterol levels in the united states: A time-sensitivity analysis from NHANES 2003-2010. Atherosclerosis 2014;235:e261.
Exclusie, niet zoekvraag	Toth, P.P. and Massaro, J. and Jones, S. and Lirette, S. and Griswold, M. and Martin, S. and Joshi, P. and D'Agostino, R. Quantitative impact of remnant lipoproteins on risk for hard CHD events: A meta-analysis of the framingham offspring and jackson heart studies. J Am Coll Cardiol 2014;63:A1460.
Exclusie, niet zoekvraag	Williams, K. and Lawler, P. and Sniderman, A.D. Implications of the selection of target markers for LDL lowering. Circ Cardiovasc Qual Outcomes 2011;4:6.

Noot 27: Behandeling lipiden

Zoekverantwoording

Database	Zoektermen		Totaal
Medline (OVID)	1	exp *Cardiovascular Diseases/ or (cardiovascular disease* or CVD or vascular disease* or vascular event* or coronary heart disease or CHD).ti,ab,kf. (2068799)	781
	2	*Cholesterol, LDL/ or ((LDL or low-density lipoprotein) adj3 (C or cholesterol)).ti,ab,kf. (56329)	
	3	(meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (358689)	
	4	randomized controlled trial.pt. or random*.ti. (566848)	
	5	Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab.m_titl. (1)	
	6	(Effects of AMG 145 on low-density lipoprotein cholesterol levels: results from 2 randomized, double-blind, placebo-controlled, ascending-dose phase 1 studies in healthy volunteers and hypercholesterolemic subjects on statins).m_titl. (1)	
	7	AMG 145, a monoclonal antibody against PCSK9, facilitates achievement of national cholesterol education program-adult treatment panel III low-density lipoprotein cholesterol goals among high-risk patients: an analysis from the LAPLACE-TIMI 57 trial.m_titl. (1)	
	8	"Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy".m_titl. (2)	
	9	5 or 6 or 7 or 8 (5)	
	10	exp *ezetimibe/ or ezetimibe*.ti,ab,kf. or PCSK9.ti,ab,kf. or *Proprotein Convertase 9/ or *Serine Endopeptidases/ or *Proprotein Convertases/ (18736)	
	Annotation: Vanaf 2017 volstaat *Proprotein Convertase 9/ als MESh term voor PCSK9		

	11 (alirocumab or evolocumab).ti,ab,kf. (438) 12 10 or 11 (18821) 13 (1 or 2) and 12 (3714) 14 limit 13 to (yr="2005 -Current" and (dutch or english)) (3073) 15 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (358689) 16 14 and 15 (174) – 152 uniek 17 randomized controlled trial.pt. or random*.ti. (566848) 18 14 and 17 (572) 19 9 and 18 (5) 20 18 not 16 (555) – 458 uniek	
Embase (Elsevier)	(('low density lipoprotein cholesterol'/exp/mj OR 'very low density lipoprotein cholesterol'/exp/mj OR (((ldl OR 'low-density lipoprotein*') NEAR/3 (c OR cholesterol)):ti,ab) OR 'cardiovascular disease'/exp/mj OR 'cardiovascular disease*':ti,ab OR cvd:ti,ab OR 'vascular disease*':ti,ab OR 'vascular event*':ti,ab OR 'coronary heart disease':ti,ab OR chd:ti,ab) AND (('ezetimibe'/exp/mj OR 'proprotein convertase 9'/exp OR 'evolocumab'/exp/mj OR 'alirocumab'/exp/mj) OR (ezetimibe*:ti,ab OR pcsk9:ti,ab OR alirocumab:ti,ab OR evolocumab:ti,ab)) AND ((dutch)/lim OR (english)/lim) AND (embase)/lim AND (2005-2017)/py NOT 'conference abstract':it) AND (('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp))) (159) – 29 uniek AND ((random*:ti OR 'randomized controlled trial'/exp) NOT 'conference abstract':it)) (465) – 122 uniek	

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Toth, 2017	Netwerk meta-analyse, gezocht tot augustus 2016
Toth, 2017	Recentere review beschikbaar
Squizzato, 2017	Recentere review beschikbaar
Soran, 2017	Intensief versus niet intensief, alleen gezocht in PubMed
Qian, 2017	Recentere review beschikbaar
Li, 2017	Recentere review beschikbaar
Khan, 2017	Recentere review beschikbaar
He, 2017	Verschillende doseringen
Eslami, 2017	Recentere review beschikbaar
AlHajri, 2017	Recentere review beschikbaar
Mueller, 2016	Recentere review beschikbaar
Cheng, 2016	Recentere review beschikbaar
Peng, 2016	Recentere review beschikbaar
Milionis, 2016	Recentere review beschikbaar
McDonagh, 2016	Recentere review beschikbaar
Lipinski, 2016	Recentere review beschikbaar
Gouni-Berthold, 2016	Recentere review beschikbaar
Araya, 2016	Geen toegang tot full text, deels geschreven in het Spaans
Battaggia, 2015	Recentere review beschikbaar
Descamps, 2015	Geen zoekactie uitgevoerd
Savarese, 2015	Recentere review beschikbaar
Thomopoulos, 2015	Recentere review beschikbaar
Zhang, 2015	Recentere review beschikbaar
Navarese, 2015	Recentere review beschikbaar
Li, 2015	Recentere review beschikbaar

Gudzune, 2014	Recentere review beschikbaar
Ambegaonkar, 2014	Recentere review beschikbaar
Gudzune, 2014	Recentere review beschikbaar
Stein, 2014	Recentere review beschikbaar
Abramson, 2011	Recentere review beschikbaar
Guyton, 2011	Recentere review beschikbaar
Mikhailidis, 2011	Recentere review beschikbaar
Angelopoulos, 2009	Recentere review beschikbaar
Mikhailidis, 2007	Recentere review beschikbaar
Catapano, 2005	Recentere review beschikbaar

Noot 28: Dyslipidemie bij (kwetsbare) ouderen

Zoekverantwoording

Database	Zoektermen	Totaal
Medline (OVID) 1946 – maart 2016	Dyslipidemias/ or Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or exp Simvastatin/ or exp Pravastatin/ or exp Rosuvastatin Calcium/ or exp Lovastatin/ or exp Atorvastatin Calcium/ or statin*.ti OR simvastatin*.ab,ti OR pravastatin*.ab,ti OR rosuvastatin*.ab,ti OR lovastatin*.ab,ti OR fluvastatin*.ab,ti OR cerivastatin*.ab,ti OR pitavastatin*.ab,ti OR atorvastatin*.ab,ti AND exp *Aged/ or aged.ti. or exp *Frail Elderly/ or *"Aged, 80 and over"/ or exp *Aging/ or exp *Geriatric Assessment/ or (elderly or geriatric or 'community dwelling' or frail* or ag?ing or septuagenarian or octogenarian or nonagenarian or centenarian or 'old people' or eldest or oldest).ti limit to (dutch or english or german) *Gebruikte filters:* Systematische reviews: (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) RCTs: (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) Observationeel: Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies) = 412	618

Embase (Elsevier)	'statin (protein)'/exp/mj OR statin*:ti OR simvastatin*:ab,ti OR pravastatin*:ab,ti OR rosuvastatin*:ab,ti OR lovastatin*:ab,ti OR fluvastatin*:ab,ti OR cerivastatin*:ab,ti OR pitavastatin*:ab,ti OR atorvastatin*:ab,ti OR 'hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp/mj AND ((dutch)/lim OR (english)/lim OR (german)/lim) AND (embase)/lim AND ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it AND ('aged'/exp/mj OR 'geriatric assessment'/exp/mj OR aged:ti OR elderly:ti OR geriatric:ti OR 'community dwelling':ti OR frail*:ti OR ageing:ti OR aging:ti OR septuagenarian:ti OR octogenarian:ti OR nonagenarian:ti OR centenarian:ti OR 'old people':ti OR eldest:ti OR oldest:ti) OR 'statin (protein)'/exp/mj OR statin*:ti OR simvastatin*:ab,ti OR pravastatin*:ab,ti OR rosuvastatin*:ab,ti OR lovastatin*:ab,ti OR fluvastatin*:ab,ti OR cerivastatin*:ab,ti OR pitavastatin*:ab,ti OR atorvastatin*:ab,ti OR 'hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp/mj AND ((dutch)/lim OR (english)/lim OR (german)/lim) AND (embase)/lim AND ('aged'/exp OR 'geriatric assessment'/exp OR aged:ti OR elderly:ab,ti OR geriatric:ab,ti OR 'community dwelling':ab,ti OR frail*:ab,ti OR ageing:ab,ti OR aging:ab,ti OR septuagenarian:ab,ti OR octogenarian:ab,ti OR nonagenarian:ab,ti OR centenarian:ab,ti OR 'old people':ab,ti OR eldest:ab,ti OR oldest:ab,ti) AND ((systematic NEAR/2 review*):ti OR 'meta analysis':ti OR cochrane:ta) OR 'statin (protein)'/exp/mj OR statin*:ti OR simvastatin*:ab,ti OR pravastatin*:ab,ti OR rosuvastatin*:ab,ti OR lovastatin*:ab,ti OR fluvastatin*:ab,ti OR cerivastatin*:ab,ti OR pitavastatin*:ab,ti OR atorvastatin*:ab,ti OR 'hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp/mj AND ((dutch)/lim OR (english)/lim OR (german)/lim) AND (embase)/lim AND ('clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR (cohort NEAR/1 (study OR studies)):ab,ti OR (case:ab,ti AND (control NEAR/1 (study OR studies)):ab,ti) OR (follow:ab,ti AND (up NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)):ab,ti OR (epidemiologic NEAR/1 (study OR studies)):ab,ti OR ('cross sectional' NEAR/1 (study OR studies)):ab,ti) AND ('aged'/exp/mj OR 'geriatric assessment'/exp/mj OR aged:ti OR elderly:ti OR geriatric:ti OR 'community dwelling':ti OR frail*:ti OR ageing:ti OR aging:ti OR septuagenarian:ti OR octogenarian:ti OR nonagenarian:ti OR centenarian:ti OR 'old people':ti OR eldest:ti OR oldest:ti) = 403	

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Review filter	
Thai, 2016	Focus op medicatie interacties
Lowe, 2015	Geen kwaliteitsbeoordeling; alleen gezocht in Medline; studies al in bovenstaande reviews
Iwere, 2015	Meerdere trials geïncludeerd met een populatie jonger dan 70 jaar. Trials met > 70 zijn reeds geïncludeerd in Savarese, 2013
Zoungas, 2014	Narratieve review
Savaraese, 2014	Erratum
Savarese, 2013	Recentere systematische review beschikbaar
Fulcher, 2013	Congres abstract
Chen, 2012	Patiënten met diabetes

Weatherley, 2011	Risicoschatting op basis van bestaande predictiemodellen
Mills, 2011	Intensivering van statinedosering
Kolovou, 2011	Narratieve review
Biffi, 2011	Alleen beroerte als uitkomst, geen RCTs geïncludeerd
Biffi, 2011	Merendeel observationele studies geïncludeerd
Berthold, 2011	Narratieve review
Lakhan, 2010	Merendeel observationele studies; onduidelijk leeftijd van patienten
Brugts, 2009	Merendeel RCT's patiënten jonger dan 70 jaar
Walker, 2008	Narratieve review
Afilalo, 2008	Patiënten jonger dan 70 jaar
Bonovas, 2007	Studie met 70-plussers reeds geïncludeerd in Teng, 2015
Raffel, 2006	Narratieve review
Law, 2006	Alleen gezocht in Medline
Hey-Hadavi, 2006	Betreft de associatie tussen verschillende doseringen van atorvastatine
Dornbrook-Lavender, 2003	Geen zoekstrategie weergegeven; geen in- en exclusie gegevens; gemiddelde leeftijd niet weergegeven, veel waarschijnlijk onder de 70 gemiddeld. Sommige studies wel al geïncludeerd in recentere SR's
Birch, 2002	Alleen gezocht in Medline; Voldoet niet aan leeftijdscriterium
Mellies, 1993	1 onderzochte statine: pravastatin en relatief oud
RCT-filter	
Wu, 2015	Cohortstudie
Wilmot, 2015	Narratieve review
Schwartz, 2015	Narratieve review
Pilotto, 2015	Patiënten met DM; associatie tussen effectiviteit van statine en voorspelde mortaliteitsrisico
Pedro-botet, 2015	Narratieve review
Hamilton-Craig, 2015	Narratieve review
Sigurdsson, 2014	Editorial
Savarese, 2014	Editorial
Reiner, 2014	Narratieve review
Fontana, 2014	Verdeling van medicatie disutility
Drewes, 2014	PROSPER-trial analysis, gestratificeerd bij homocysteine niveaus
Stender, 2013	Geen vergelijkende groep
Stender, 2013	Vergelijking tussen twee statines in verschillende doseringen; geen placebo gegeven
Rizzo, 2013	Narratieve review
Lloyd, 2013	Studie (PROSPER) reeds geïncludeerd
Bhardwaj, 2013	Narratieve review
Sicras-Mainar, 2012	Cohortstudie
Schiattarellla, 2012	Narratieve review
Chokshi, 2012	Voorspellers voor het gebruik van een statine
Shao, 2011	Narratieve review
Szadkowska, 2010	Narratieve review
Gransbo, 2010	Cohortstudie
Fricker, 2009	Editorial
Shepherd, 2004	Editorial; beschrijving van een andere studie
Yaffe, 2002	Cohortstudie
Jackevicius, 2002	Cohortstudie
Houx, 2002	Baseline gegevens van reeds geïncludeerde studie (PROSPER)
Benner, 2002	Cohortstudie
Ito, 2001	Vergelijking tussen verschillende doseringen
Chikamori, 2000	Observationele studie
Campeau, 1999	Geen relevante uitkomsten gerapporteerd

Miettinen, 1997	Patiënten waren maximaal 70 jaar oud
Lansberg, 1995	Geen vergelijking
Santinga, 1994	Geen relevante uitkomsten gerapporteerd
LaRosa, 1994	Geen relevante uitkomsten gerapporteerd

Noot 29: Bloeddrukmeting

Zoekverantwoording

Database	Zoektermen	Totaal
Medline (OVID) Div.: 2005-juli 2017; SR: 2012-juli 2017 Engels	1 blood pressure determination/ or blood pressure monitoring, ambulatory/ or exp Sphygmomanometers/ or ABPM.ti,ab,kf. or AOBP.ti,ab,kf. or (("blood pressure" or bp) adj3 (measur* or monitor* or automat*)).ti,ab,kf. (60571) 2 *"Home Care Services"/ or exp General Practice/ or Physicians' Offices/ or "Office Visits"/ or (home or office or "24" or ambula* or practice or ABPM or AOPM).ti,ab,kf. (1869131) 3 1 and 2 (19098) 4 Prognosis/ or reference values/ or prognos*.ti. or ("reference value*" or "normative value*" or threshold*).ti,ab,kf. or (cut-off or cutoff).ti,ab,kf. or ("30" adj min*).ti,ab,kf. (1056424) 5 3 and 4 (2567) 6 limit 5 to (english language and yr="2012 -Current") (600) 7 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (335728) 8 6 and 7 (19) 9 (AOBP or (Automated adj office)).ti,ab,kf. (95) 10 1 and 9 (88) 11 limit 10 to (english language and yr="2005 -Current") (76) – 71 uniek 12 8 and 11 (1) = SR over AOBP (in beide files)	34 SR en 76 AOBP
Embase (Elsevier)	"((((('blood pressure measurement'/mj OR 'blood pressure monitoring'/exp/mj OR 'blood pressure meter'/exp/mj) OR (abpm:ti,ab OR aobp:ti,ab OR ((('blood pressure' OR bp) NEAR/3 (measur* OR monitor* OR automat*)):ti,ab))) AND (('home care'/exp/mj OR 'general practice'/exp OR 'health care facility'/exp OR 'ambulatory monitoring'/exp) OR (('blood pressure' OR bp) NEAR/3 (measur* OR monitor* OR automat*)):ti,ab) AND ('prognosis'/exp/mj OR 'reference value'/exp/mj OR prognos*:ti OR 'reference value*':ti,ab OR 'normative value*':ti,ab OR threshold*:ti,ab OR 'cut off':ti,ab OR cutoff:ti,ab OR (('30' NEAR/1 min*):ti,ab)) NOT 'conference abstract':it AND (english)/lim AND (embase)/lim AND (2012-2017)/py) AND (('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp))) (25) – 15 uniek OR ((('blood pressure measurement'/mj OR 'blood pressure monitoring'/exp/mj OR 'blood pressure meter'/exp/mj) OR (abpm:ti,ab OR aobp:ti,ab OR ((('blood pressure' OR bp) NEAR/3 (measur* OR monitor* OR automat*)):ti,ab))) AND (aobp:ti,ab OR ((automated NEAR/1 office):ti,ab)) NOT 'conference abstract':it AND (english)/lim AND (embase)/lim AND (2005-2017)/py) (63) – 4 uniek	

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Reviews	
Albasri, 2017	Bloeddruk gemeten bij de apotheek versus door de huisarts
Blom, 2015	Betreft een studieprotocol
Reino-Gonzalez, 2017	Vergelijking tussen ABPM en spreekkamermetingen

Diverse designs	
Andreadis, 2017	Interval tussen bloeddrukmeting: 1 minuut
Jegatheswaran, 2017	Interval tussen bloeddrukmeting: 1 à 2 minuten (1 referentie gevonden [Culleton 2006])
Rinfret, 2017	Interval tussen bloeddrukmeting: 1 minuut
Filipovsky, 2016	Patiënten met hypertensie (97,5% gebruikte antihypertensiva)
Wohlfahrt, 2016	Interval tussen bloeddrukmeting: 1 minuut
Padwal, 2015	Patiënten met hypertensie; vergelijking apotheek versus ABPM
Myers, 2014	Case report en narratieve review
Edwards, 2013	Interval tussen bloeddrukmeting: 1 minuut
van der Wel, 2013	Letter to the editor (commentaar) (1 referentie gevonden [Van der Wel 2011])
Andreadis, 2012	Interval tussen bloeddrukmeting: 1 minuut
Myers, 2012	Interval tussen bloeddrukmeting: 1 à 2 minuten
Myers, 2012	Zelfde trial als vorige
Andreadis, 2011	Interval tussen bloeddrukmeting: 1 minuut
Godwin, 2011	Interval tussen bloeddrukmeting: 1 minuut
Lamarre-Cliche, 2011	Interval tussen bloeddrukmeting: 1 minuut
Myers, 2011	Interval tussen bloeddrukmeting: 1 à 2 minuten
Myers, 2009	Interval tussen bloeddrukmeting: 1 à 2 minuten
Myers, 2008	Interval tussen bloeddrukmeting: 1 à 2 minuten

Noot 34: Bloeddrukstreefwaarden bij behandeling van hypertensie bij (kwetsbare) ouderen

Zoekverantwoording

Database	Zoektermen		Totaal
Medline (OVID) 1948-apr. 2016 Engels	1	(exp Hypertension/ or hypertensi*.ti,ab. or 'blood pressure'.ti,ab. or hbp.ti,ab. or Blood Pressure/) and (Antihypertensive Agents/ or antihypertensi*.ti,ab.) (62711)	1491
	2	exp Aged/ or aged.ti. or exp Frail Elderly/ or "Aged, 80 and over"/ or exp Aging/ or exp Geriatric Assessment/ or (elderly or geriatric or 'community dwelling' or frail* or ag?ing or septuagenarian* or octogenarian* or nonagenarian* or centenarian* or 'old people' or eldest or oldest or "biological age").ti,ab. (2834312)	
	3	1 and 2 (19119)	
	4	limit 3 to english (16115)	
	15	*Reference Values/ or (target* or threshold or (reference adj2 value*)).ab. /freq=2 or (goal* or target* or (reference adj2 value*)).ti. or intensi*.ti,ab. or ((pressure or BP) adj3 goal*).ab. /freq=2 or (elderly or "very old" or "oldest old" or "80 years").ti. (1054271)	
	16	4 and 15 (2710)	
	17	(meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (275361)	
	18	16 and 17 (98)	
	19	(randomized controlled trial/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or randomized controlled trial.pt. or random*.ti,ab. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (991935)	
	20	16 and 19 (1044)	
	21	20 not 18 (978)	

Embase (Elsevier)	'aged'/exp/mj OR 'geriatric assessment'/exp/mj OR aged:ti OR elderly:ab,ti OR geriatric*:ab,ti OR 'community dwelling':ab,ti OR frail*:ab,ti OR ageing:ab,ti OR aging:ab,ti OR septuagenarian*:ab,ti OR octogenarian*:ab,ti OR nonagenarian*:ab,ti OR centenarian*:ab,ti OR 'old people':ab,ti OR eldest:ab,ti OR oldest:ab,ti OR 'biological age' OR (individual NEAR/2 (patient* OR participant*) NEAR/2 data*):ab,ti AND (english)/lim AND (embase)/lim AND ('hypertension'/exp/mj OR 'blood pressure'/exp/mj OR hypertensi*:ab,ti OR 'blood pressure':ab,ti OR hbp:ab,ti) AND ('antihypertensive agent'/exp/mj OR antihypertensi*:ab,ti) AND ('reference value'/exp OR goal*:ti OR target*:ti OR threshold:ti OR (reference NEAR/2 value*):ti OR intensi*:ab,ti OR elderly:ti OR 'very old':ti OR 'oldest old':ti OR '80 years':ti) 'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp) AND ('randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it (77) 'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp) (658)	

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Review filter	
Parsons, 2016	Gemiddelde leeftijd van 65 jaar of ouder; effect van behandeling op beroerte
Peters, 2014	Type antihypertensiva
Goeres, 2014	Geen meta-analyse; leeftijd niet allen boven 70 jaar; geen RoB-beoordeling
Sundstrom, 2014	Data gestratificeerd op risico en niet op leeftijd
Ahola, 2012	Observationele studie met data van twee databases en jonger dan 70 jaar; geen subgroepanalyse
Schall, 2011	Geen evidence-tabel beschikbaar; geen bekende tool gebruikt voor Risk of Bias beoordeling, alleen benoemd items worden bekeken. Echter, er wordt in de tekst geen oordeel over gegeven.
Bejan-Angoulvant, 2010	Niet systematisch gezocht, onduidelijk ook tot wanneer trials zijn geïncludeerd
Musini, 2009	Leeftijdsgrens 60 jaar of ouder
Bulpitt, 2003	Resultaten van een pilot van de HYVET-studie, die reeds is geïncludeerd
Messerli, 2001	Alleen gezocht in Medline en tot juni 1999
Gueyffier, 1999	Geïncludeerd studies zijn ook geïncludeerd door Schall, 2011
Pearce, 1995	Recentere reviews komen in aanmerking
RCT-filter	
Omboni, 2015	Vergelijking tussen twee type antihypertensiva
Moonen, 2015	Stoppen met antihypertensiva

Tinetti, 2014	Observationele studie met data over hart- en vaatziekten en mortaliteit gerapporteerd (data reeds beschikbaar uit RCT's)
Beckett, 2014	Trial reeds geïncludeerd, rapportage van niet relevant subgroepanalyse
Zanchetti, 2014	Studieprotocol
Williamson, 2014	Patiënten met diabetes en jonger dan 70 jaar
Vagholkar, 2014	Geen relevante uitkomstmaten gerapporteerd
Tinetti, 2014	Geen relevante uitkomstmaten
Reboldi, 2014	Totale mortaliteit en hart- en vaatziekten in 1 uitkomstmaat gerapporteerd; gemiddelde leeftijd voor drie van vier groepen onder 70 jaar
Mohebi, 2014	Gemiddelde leeftijd onder 70 jaar en geen subgroepanalyse beschikbaar; observationele studies, geen propensity score analyse
Margolis, 2014	Patiënten met diabetes en jonger dan 70 jaar
Peters, 2013	Trial reeds geïncludeerd; geen relevante uitkomstmaat
Zhang, 2013	Geen relevante uitkomstmaten
White, 2013	Studieprotocol
Weir, 2013	Geen relevante uitkomstmaten
Beckett, 2012	Open label extensie van een trial, met als vergelijking vroeg starten versus laat starten
Zhang, 2011	Subgroepanalyse: > 65 of ≤ 65
Group, 2010	Patiënten met diabetes en jonger dan 70 jaar
Bangalore, 2010	Patiënten die een statine krijgen
Aronow, 2009	Letter to editor/reactie van auteur
Verdecchia, 2009	Alleen subgroep analyse beschikbaar; reeds volledige artikel kunnen includeren
Tardif, 2008	Geen relevante uitkomstmaten
Rakugi, 2008	Narratieve review
Ogiharam, 2008	Vergelijking tussen twee anithypertensiva
Flack, 2008	Geen vergelijkende groep
Ferguson, 2008	Geen relevante uitkomstmaten
Patel, 2007	Patiënten met diabetes
Kintscher, 2007	Vergelijking tussen verschillende antihypertensiva
Kabakci, 2007	Risicofactoren voor hart- en vaatziekten
Fagard, 2007	Relevante data reeds geïncludeerd
Eijkelkamp, 2007	Geen relevante uitkomstmaten
Agostini, 2007	Intensiteit van behandeling gedefinieerd aan de hand van de hoeveelheid klassen van antihypertensiva werden gebruikt
Roumie, 2006	Geen relevante uitkomstmaten
Perkovic, 2006	Geen relevante uitkomstmaten
Group, 2005	Studieprotocol
Gard, 2004	Narratieve review
Ferrari, 2004	Geen relevante uitkomstmaten
Lithell, 2004	Meerderheid van placebogroep kreeg add-on antihypertensiva binnen vier maanden na het starten van de trial
Degl'Innoncenti, 2004	Meerderheid van placebogroep kreeg add-on antihypertensiva binnen vier maanden na het starten van de trial
Mancia, 2003	Vergelijking tussen verschillende antihypertensiva
Jungmann, 2003	Narratieve review
Jonsson, 2003	Geen relevante uitkomstmaten gerapporteerd (kosteneffectiviteit in Zweden)
Lithell, 2003	Meerderheid van placebogroep kreeg add-on antihypertensiva binnen vier maanden na het starten van de trial
Camisasca, 2002	Uitvoering van een richtlijn
Hansson, 2001	Narratieve review
Emeriau, 2001	Vergelijking tussen medicamenten

Wassertheil-Smoller, 2000	Associatie tussen BMI, hypertensie en mortaliteit
Wang, 2000	Effectschatter met betrouwbaarheidsinterval niet te extraheren (wordt alleen in een grafiek weergegeven)
Trenkwalder, 2000	Narratieve review
Perry, 2000	Subgroepanalyse niet beschikbaar
Ogihara, 2000	Geen originele beschrijving van een studie
Lindholm, 2000	Vergelijking tussen verschillende hypertensiva
Lassila, 2000	Follow-up na een trial
Bulpitt, 2000	Vergelijking van medicamenten bij hoge diastolische bloeddruk
Brown, 2000	Vergelijking tussen antihypertensiva
Fagard, 1999	Originele studie geïncludeerd
Alli, 1999	SBP en SBP als voorspellers van mortaliteit
Berlowitz, 1998	Ontwikkeling van een soort predictie model over behandeling van hypertensie
Zeng, 1998	Effect van medicatie op syncope
Winther, 1998	Patiënten met cognitieve stoornissen en zonder hypertensie
Whelton, 1998	Patiënten reeds op medicatie en vervolgens het effect van gewichtsverlies en beperkte zoutinname
Staessen, 1998	Originele studie geïncludeerd
Savage, 1998	Ontwikkeling van diabetes tijdens RCT
Pahor, 1998	Patiënten met hypertensie en nierfalen
Kostis, 1998	Over het stoppen van medicatie
Hansson, 1993	Narratieve review
Aagaard, 1984	Narratieve review
Welzel, 1982	Narratieve review

Noot 35: Welk hypertensivum bij (kwetsbare) ouderen (> 70 jaar)

Zoekverantwoording

Database	Zoektermen		Totaal
Medline (OVID) 2000-heden Engels	1	exp antihypertensive agents/ or exp calcium channel blockers/ or exp Angiotensin-Converting Enzyme Inhibitors/ or exp Angiotensin Receptor Antagonists/ or exp Thiazides/ or exp Adrenergic beta-Antagonists/ or (antihypertensi* or "Calcium channel blocker*" or ACE-inhibitors or "angiotensin-receptor blocker*" or thiazides or beta-blocker*).ti,ab. or Hypertension/dt (362454)	369
	2	exp *Aged/ or aged.ti. or exp *Frail Elderly/ or *"Aged, 80 and over"/ or (elderly or geriatric or 'community dwelling' or frail* or ag?ing or septuagenarian* or octogenarian* or nonagenarian* or centenarian* or 'old people' or eldest or oldest or "biological age").ti. (234786)	
	3	1 and 2 (5489)	
	4	limit 3 to english language (4495)	
	5	(meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (285410)	
	6	4 and 5 (89)	
	7	(exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1584180)	
	8	4 and 7 (1541)	
	9	comparative study.pt. or (compar* or vs or versus).ti. (2040335)	
	10	8 and 9 (402)	
	11	limit 10 to yr="2000 -Current" (275)	
	12	limit 6 to yr="2000 -Current" (83)	
	13	11 not 12 (272)	

Embase (Elsevier)	'calcium channel blocking agent'/exp/mj OR 'thiazide diuretic agent'/exp/mj OR 'beta adrenergic receptor blocking agent'/exp/mj OR 'calcium channel blocker*':ab,ti OR 'ace inhibitors':ab,ti OR 'angiotensin-receptor blocker*':ab,ti OR thiazides:ab,ti OR 'beta blocker*':ab,ti AND ('hypertension'/exp/mj OR 'blood pressure'/exp/mj OR hypertensi*:ab,ti OR 'blood pressure':ab,ti OR hbp:ab,ti) OR 'hypertension'/exp/mj/dm_dt OR antihypertensi*:ab,ti OR 'antihypertensive agent'/exp/mj AND ('aged'/exp/mj OR 'geriatric assessment'/exp/mj OR aged:ti OR elderly:ti OR geriatric*:ti OR 'community dwelling':ti OR frail*:ti OR ageing:ti OR aging:ti OR septuagenarian*:ti OR octogenarian*:ti OR nonagenarian*:ti OR centenarian*:ti OR 'old people':ti OR eldest:ti OR oldest:ti) AND (english)/lim AND (embase)/lim AND 'meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp)) (110) – 61 SR AND ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it AND (compar*:ti OR vs:ti OR versus:ti OR 'comparative study'/exp) (204) – 128 RCT	

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Review filter	
Peters, 2014	Merendeel cohortstudies geïncludeerd; 1 RCT vergeleek met placebo
Coca, 2013	Narratieve review
Zeglin, 2009	Narratieve review
Hebert, 2008	Vergeleken met placebo (bij drie trials met een gemiddelde leeftijd > 70)
Messerli, 1998	Gezocht in januari, 1998; leeftijd vanaf 60 jaar
RCT-filter	
Omboni, 2015	Re-analyse van twee RCT; niet systematisch gezocht
Chien, 2015	Cohortstudie
Omboni, 2014	Data van twee RCT's, niet systematisch gezocht
Matsui, 2014	Subgroepanalyse gestratificeerd op geslacht van een trial reeds geselecteerd
Graham, 2014	Vergelijking tussen verschillende angiotensine II-receptorantagonisten
Cohen, 2011	Narratieve review
Hajjar, 2005	Cohortstudie met vergelijking versus geen medicatie; geen propensity score matching
Papademetriou, 2004	Vergeleken met placebo
Ekbom, 2004	Subgroep analyse STOP trial reeds geïncludeerd
Pessina, 2001	Patiënten tussen 60 en 80 geïncludeerd; gemiddelde leeftijd < 70
Ogihara, 2000	NICS-EH studie; gemiddelde leeftijd < 70 jaar
Ogihara, 2000	PATE-hypertension studie; gemiddelde leeftijd < 70 jaar
Lindholm, 2000	Subgroep analysis: diabetes op baseline
Kuwajima, 2000	Conference abstract
Calvo, 2000	Gemiddelde leeftijd patiënten < 70 jaar

Noot 36: Stoppen hypertensiva bij (kwetsbare) ouderen

Zoekverantwoording

Database	Zoektermen		Totaal
Medline (OVID) 1980-apr. 2016 Engels, Nederlands	4	(exp Hypertension/ or hypertensi*.ti,ab. or 'blood pressure'.ti,ab. or hbp.ti,ab. or Blood Pressure/) and (Antihypertensive Agents/ or antihypertensi*.ti,ab.) (62171)	431
	5	Withholding Treatment/ or (cessation or stop* or termina* or cease or ceasing or discontinua* or withdrawal).ti,ab,kf. (755452)	
	6	4 and 5 (2939)	
	7	limit 6 to (yr="1980 -Current" and (dutch or english)) (2518)	
	8	(meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (266238)	
	9	7 and 8 (102)	
	10	*Withholding Treatment/ or (cessation or stop* or termina* or cease or ceasing or discontinua* or withdrawal).ti. or ((treatment or drugs or therapy or agent*) adj6 (cessation or stop* or termina* or cease or ceasing or discontinua* or withdrawal)).ti,ab,kf. (165828)	
	11	exp Aged/ or aged.ti. or exp Frail Elderly/ or "Aged, 80 and over"/ or exp Aging/ or exp Geriatric Assessment/ or (elderly or geriatric or 'community dwelling' or frail* or ag?ing or septuagenarian* or octogenarian* or nonagenarian* or centenarian* or 'old people' or eldest or oldest or "biological age").ti,ab. (2818704)	
	12	10 or 11 (2960984)	
	13	9 and 12 (49)	
	15	7 and 11 (941)	
	16	(exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1526214)	
	17	15 and 16 (557)	
	18	Withholding Treatment/ or (cessation or stop* or termina* or cease or ceasing or discontinua* or withdrawal).ti. or ((treatment or drugs or therapy or agent*) adj6 (cessation or stop* or termina* or cease or ceasing or discontinua* or withdrawal)).ti,ab,kf. (170641)	
	19	17 and 18 (211)	
	21	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies) (2522985)	
	22	15 and 21 (365)	
	23	Withholding Treatment/ or (cessation or stop* or termina* or cease or ceasing or discontinua* or withdrawal).ti. or ((treatment or drugs or therapy or agent*) adj6	

	(cessation or stop* or termina* or cease or ceasing or discontinua* or withdrawal)).ti,ab,kf. (170641) 24 22 and 23 (151) 25 13 or 19 (255) 26 24 not 25 (72) 29 13 or 19 or 24 (327) 31 19 not 13 (206) – 203 uniek	
Embase (Elsevier)	'blood pressure'/exp/mj OR hypertensi*:ab,ti OR 'blood pressure':ab,ti OR hbp:ab,ti AND ('antihypertensive agent'/exp/mj OR antihypertensi*:ab,ti) AND ('treatment withdrawal'/exp OR cessation:ab,ti OR stop*:ab,ti OR termina*:ab,ti OR cease:ab,ti OR ceasing:ab,ti OR discontinua*:ab,ti OR withdrawal:ab,ti) AND ((dutch)/lim OR (english)/lim) AND (embase)/lim AND (1980-2016)/py NOT 'conference abstract':it AND ('meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp) AND ('treatment withdrawal'/exp/mj OR cessation:ti OR stop*:ti OR termina*:ti OR cease:ti OR ceasing:ti OR discontinua*:ti OR withdrawal:ti OR ((treatment OR drugs OR therapy OR agent*) NEAR/6 (cessation OR stop* OR termina* OR cease OR ceasing OR discontinua* OR withdrawal)):ab,ti OR 'aged'/exp/mj OR 'geriatric assessment'/exp/mj OR aged:ti OR elderly:ab,ti OR geriatric*:ab,ti OR 'community dwelling':ab,ti OR frail*:ab,ti OR ageing:ab,ti OR aging:ab,ti OR septuagenarian*:ab,ti OR octogenarian*:ab,ti OR nonagenarian*:ab,ti OR centenarian*:ab,ti OR 'old people':ab,ti OR eldest:ab,ti OR oldest:ab,ti OR 'biological age' OR (individual NEAR/2 (patient* OR participant*) NEAR/2 data*):ab,ti) (51) – SR – 29 uniek 'blood pressure'/exp/mj OR hypertensi*:ab,ti OR 'blood pressure':ab,ti OR hbp:ab,ti AND ('antihypertensive agent'/exp/mj OR antihypertensi*:ab,ti) AND ('treatment withdrawal'/exp OR cessation:ab,ti OR stop*:ab,ti OR termina*:ab,ti OR cease:ab,ti OR ceasing:ab,ti OR discontinua*:ab,ti OR withdrawal:ab,ti) AND ((dutch)/lim OR (english)/lim) AND (embase)/lim AND (1980-2016)/py AND ('aged'/exp/mj OR 'geriatric assessment'/exp/mj OR aged:ti OR elderly:ab,ti OR geriatric*:ab,ti OR 'community dwelling':ab,ti OR frail*:ab,ti OR ageing:ab,ti OR aging:ab,ti OR septuagenarian*:ab,ti OR octogenarian*:ab,ti OR nonagenarian*:ab,ti OR centenarian*:ab,ti OR 'old people':ab,ti OR eldest:ab,ti OR oldest:ab,ti OR 'biological age' OR (individual NEAR/2 (patient* OR participant*) NEAR/2 data*):ab,ti) AND ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR 'comparative study'/exp OR placebo*:ab,ti) NOT 'conference abstract':it AND ('treatment withdrawal'/exp OR cessation:ti OR stop*:ti OR termina*:ti OR cease:ti OR ceasing:ti OR discontinua*:ti OR withdrawal:ti OR ((treatment OR drugs OR therapy OR agent*) NEAR/6 (cessation OR stop* OR termina* OR cease OR ceasing OR discontinua* OR withdrawal)):ab,ti), (66) RCT – 24 uniek 'blood pressure'/exp/mj OR hypertensi*:ab,ti OR 'blood pressure':ab,ti OR hbp:ab,ti AND ('antihypertensive agent'/exp/mj OR antihypertensi*:ab,ti) AND ('treatment withdrawal'/exp OR cessation:ab,ti OR stop*:ab,ti OR termina*:ab,ti OR cease:ab,ti OR ceasing:ab,ti OR discontinua*:ab,ti OR withdrawal:ab,ti) AND ((dutch)/lim OR (english)/lim) AND (embase)/lim AND (1980-2016)/py NOT 'conference abstract':it **AND 'major clinical study'/de** AND ('aged'/exp/mj OR 'geriatric assessment'/exp/mj OR aged:ti OR elderly:ab,ti OR geriatric*:ab,ti OR 'community dwelling':ab,ti OR frail*:ab,ti OR ageing:ab,ti OR aging:ab,ti OR septuagenarian*:ab,ti OR octogenarian*:ab,ti OR nonagenarian*:ab,ti OR centenarian*:ab,ti	

	OR 'old people':ab,ti OR eldest:ab,ti OR oldest:ab,ti OR 'biological age' OR (individual NEAR/2 (patient* OR participant*) NEAR/2 data*):ab,ti) (61) MCS – 54 uniek	

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Review filter	
Maddison, 2011	Review naar de preventieve medicatie in palliatieve patiënten. Richt zich niet specifiek op antihypertensiva, niet specifiek ouderen
Weber, 2001	Beschrijving van de studie van Nelson, 2001
Nelson, 2001	Systematische review naar voorspellers van het behouden van adequate bloeddruk na stoppen van antihypertensiva
Froom, 1997	Oude review met niet alleen RCT geïncludeerd en geen risico op bias beoordeling
RCT-filter	
Moonen, 2016	Subgroepanalyse van de DANTE-studie (RCT). Kijkt naar stoppen antihypertensiva bij patiënten met milde cognitieve beperkingen en orthostatische hypotensie op orthostatische hypotensie
Moonen, 2015	Cross-sectionele studie op de baseline data van de DANTE-studie. Kijkt naar de associatie tussen BP-metingen en symptomen van apathie en depressie in ouderen met verschillende maten van functioneren
Foster-Dingley, 2015	Subgroep van de DANTE-studie. Kijkt naar CBF-verandering na 4 maanden. Geen andere uitkomsten geïncludeerd
Hajjar, 2013	Geen controlegroep, alle patiënten probeerde te stoppen
Thien, 2008	Beschrijving van een Engelstalig artikel, HYVAT-studie
Teichert, 2007	Cohortstudie. Gaat alleen over Beta-blokkers
Van Kraaij, 2000	Betreft geen antihypertensiva
Van Kraaij, 1999	Slechts 20 patiënten geïncludeerd, 7 in de controlegroep en 13 in de interventie. Richt zich op de postprandiale hypotensie
Espeland, 1999	Tone studie; 80% van het cohort < 70 jaar
Kostis, 1998	Tone studie; 80% van het cohort < 70 jaar
Fotherby, 1994	Geen RCT (n = 47). Patiënten die niet stopte (n = 13) met de antihypertensiva hadden een te hoge bloeddruk op baseline of wilden niet vaker naar het ziekenhuis komen
Ekbom, 1994	Geen RCT, cohort waarbij alle patiënten stopten met therapie en over de tijd gevolgd werden. Patiënten konden van de medicatie afblijven of weer beginnen
Observationele studies filter	
Correa, 2014	Population-based prospective cohort study. > 60 jaar oud bewoners. Leeftijd van de deelnemers was 69.1
Breekveldt-Postma, 2008	Cohortstudie, 77.193 deelnemers, Overgrote gedeelte van de deelnemers < 70 jaar
Nadal, 1994	Alle patiënten probeerde te stoppen, geen vergelijkende studies
Lernfelt, 1990	Cohort, 25 van de 32 patiënten stopten met het gebruik van antihypertensiva, waarvan 14 ook daadwerkelijk van de medicatie afbleven. Oude studie, geen goede vergelijking

Noot 38: Starten met trombocytenaggregatieremmers bij (kwetsbare) ouderen

Zoekverantwoording

Database	Zoektermen		Totaal
Medline (OVID) Engels, Nederlands	1	cardiovascular diseases/ or exp heart diseases/ or exp vascular diseases/ (2002555)	410
	2	((cerebrovascular or cardiovascular or heart or vascular) adj3 (disease* or disorder* or event*)).ti,ab. (328148)	
	3	((myocard* adj2 infarct*) or "cerebral vascular accident" or CVA or stroke or TIA).ti,ab. (308796)	
	4	1 or 2 or 3 (2161270)	
	5	exp Platelet Aggregation Inhibitors/ (94609)	
	6	Aspirin/ (39706)	
	7	exp Dipyridamole/ (7437)	
	8	Prasugrel Hydrochloride/ (802)	
	9	(dipyridamol or clopidogrel or aspirin* or prasugrel or ticagrelor or "acetylsalicylic acid*" or "Platelet Aggregation Inhibitor*").ti,ab. (51763)	
	10	5 or 6 or 7 or 8 or 9 (113677)	
	11	4 and 10 (46872)	
	17	primary prevention/ or secondary prevention/ or ((primary or secondary) adj3 prevention).ti,ab. or prophyla*.ti,ab. (180774)	
	18	11 and 17 (5221)	
	19	limit 18 to (dutch or english) (4290)	
	20	exp Aged/ or aged.ti. or exp Frail Elderly/ or "Aged, 80 and over"/ or exp Aging/ or exp Geriatric Assessment/ or (elderly or geriatric or 'community dwelling' or frail* or ag?ing or septuagenarian or octogenarian or nonagenarian or centenarian or 'old people' or eldest or oldest).ti,ab. or (individual adj2 (patient* or participant*) adj1 data*).ti,ab. (Breed ouderenfilter) (2766368)	
	21	19 and 20 (1555)	
	22	Placebos/ or placebo*.tw. or Double-Blind Method/ or Single-Blind Method/ or (individual adj2 (patient* or participant*) adj1 data*).ti,ab. (258963)	
	23	21 and 22 (253)	
	24	(meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (256072)	
	25	23 and 24 (29) – 28 uniek	
	31	23 not 25 (224) – 223 uniek	
Embase (Elsevier)	'primary prevention'/exp OR 'prophylaxis'/de OR 'heart infarction prevention'/de OR 'secondary prevention'/de OR ((primary OR secondary) NEAR/3 prevention):ab,ti OR prophyla*:ab,ti OR prevent*:ti AND ('placebo'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR placebo*:ab,ti OR (individual NEAR/2 (patient*i OR participant*) NEAR/2 data*):ab,ti) AND ('cardiovascular disease'/exp/mj OR (myocard* NEAR/2 infarct*):ab,ti OR 'cerebral vascular accident':ab,ti OR stroke:ab,ti OR ((cerebrovascular OR cardiovascular OR heart OR vascular) NEAR/3 (disease* OR disorder* OR event*)):ab,ti) AND ('antithrombocytic agent'/exp/mj OR dipyridamol:ab,ti OR clopidogrel:ab,ti OR prasugrel:ab,ti OR ticagrelor:ab,ti OR 'acetylsalicylic acid':ab,ti OR 'platelet aggregation inhibitors':ab,ti)		

	AND ('aged'/exp OR 'geriatric assessment'/exp OR aged:ti OR elderly:ab,ti OR geriatric*:ab,ti OR 'community dwelling':ab,ti OR frail*:ab,ti OR ageing:ab,ti OR aging:ab,ti OR septuagenarian*:ab,ti OR octogenarian*:ab,ti OR nonagenarian*:ab,ti OR centenarian*:ab,ti OR 'old people':ab,ti OR eldest:ab,ti OR oldest:ab,ti OR (individual NEAR/2 (patient*i OR participant*) NEAR/2 data*):ab,ti) AND 'conference abstract':it AND ((dutch)/lim OR (english)/lim) AND (embase)/lim AND 'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp)) (29) – 20 uniek Overig: 226 – 139 uniek	

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Review filter	
Sarbacker, 2016	Gezocht in 1 database; gedetailleerde zoekstrategie niet beschikbaar; geen beoordeling van Risk of Bias
Kwok, 2015	Betreft een stroke subtype (lacunar)
Sutcliffe, 2013	Trials includeerde niet alleen 70 jaar of ouder; mogelijk subgroep analyse was niet te graderen uit 1 trial (vroegtijdig gestopt)
Bartolucci, 2011	Review is geïncludeerd in de review van Sutcliffe (no. 6)
Berger, 2009	Geïncludeerd trials, alle met een gemiddelde leeftijd jonger dan 70 jaar
Antithrombotic trialists, 2009	Alleen data van trials aangesloten bij dit consortium is meegenomen
Critical Leg Ischaemia Prevention Study, 2007	RCT, geen systematische review; reeds geïncludeerd in Sutcliffe, 2013
Bartolucci, 2006	Recentere reviews beschikbaar
Leonardi-Bee, 2005	Interventie: dipyridamole met of zonder aspirine
Edelman, 2003	Recentere reviews beschikbaar
Bredie, 2002	Recentere reviews beschikbaar
RCT-filter	
Van Kruijsdijk, 2015	WHS is reeds geïncludeerd in de review van Sutcliffe, 2013
Ikeda, 2014	Niet placebogecontroleerd
Rist, 2013	WHS is reeds geïncludeerd in de review van Sutcliffe, 2013
ASPREE	Studieprotocol
Robinson, 2012	Associatie tussen risicofactoren en CVD
Dorresteijn, 2011	Predictiemodel bij verschillende schema's van voorschrijven
Jardine, 2010	Subgroepanalyse RCT
Fowkes, 2010	Reeds geïncludeerd in Sutcliffe, 2013
Fowkes, 2009	Reeds geïncludeerd in Sutcliffe, 2013
Ogawa, 2008	Niet placebogecontroleerd
Nelson, 2008	Geen relevante uitkomsten gerapporteerd
Belch, 2008	Reeds geïncludeerd in Sutcliffe, 2013
Ridker, 2005	Reeds geïncludeerd in Sutcliffe, 2013
Nelson, 2003	Studieprotocol
Meade, 2000	Reeds geïncludeerd in Sutcliffe, 2013

Meade, 1998	Reeds geïncludeerd in Sutcliffe, 2013
Forbes, 1998	Beschrijving van bestaande trial (geen origineel onderzoek)
Anonymous, 1998	Reeds geïncludeerd in Sutcliffe, 2013
Forbes, 1997	Beschrijving van bestaande trial (geen origineel onderzoek) & vergelijking: dipyridamole met of zonder aspirine
Sivenius, 1993	Vergelijking: dipyridamole met of zonder aspirine
Sivenius, 1992	Vergelijking: dipyridamole met of zonder aspirine
Juul-Moller, 1992	Patiënten gemiddeld jonger dan 70 (30 to 80 geïncludeerd); geen subgroepanalyses beschikbaar
Ridker, 1991	Zelfde populatie als in Anonymous, 1989
Ridker, 1991	Zelfde populatie als in Anonymous, 1989
Manson, 1990	Reeds geïncludeerd in Sutcliffe, 2013
Anonymous, 1989	Reeds geïncludeerd in Sutcliffe, 2013
Breddin, 1980	Alleen patiënten jonger dan 71 geïncludeerd

Noot 39: Stoppen met trombocytenaggregatieremmers bij (kwetsbare) ouderen

Zoekverantwoording

Database	Zoektermen		Totaal
Medline (OVID) 1948-juni 2016 Engels, Nederlands	1	cardiovascular diseases/ or exp heart diseases/ or exp vascular diseases/ (2062204)	329
	2	((cerebrovascular or cardiovascular or heart or vascular) adj3 (disease* or disorder* or event*)).ti,ab. (342248)	
	3	((myocard* adj2 infarct*) or "cerebral vascular accident" or CVA or stroke or TIA).ti,ab. (320739)	
	4	1 or 2 or 3 (2227793)	
	5	exp Platelet Aggregation Inhibitors/ (96691)	
	6	Aspirin/ (40575)	
	7	exp Dipyridamole/ (7512)	
	8	Prasugrel Hydrochloride/ (885)	
	9	(dipyridamol or clopidogrel or aspirin* or prasugrel or ticagrelor or "acetylsalicylic acid*" or "Platelet Aggregation Inhibitor*").ti,ab. (53313)	
	10	5 or 6 or 7 or 8 or 9 (116336)	
	11	4 and 10 (48358)	
	12	Withholding Treatment/ or (cessation or stop* or termina* or cease or ceasing or discontinua* or withdrawal).ti,ab,kf. (765084)	
	13	11 and 12 (2606)	
	14	limit 13 to (dutch or english) (2293)	
	15	exp Aged/ or aged.ti. or exp Frail Elderly/ or "Aged, 80 and over"/ or exp Aging/ or exp Geriatric Assessment/ or (elderly or geriatric or 'community dwelling' or frail* or ag?ing or septuagenarian or octogenarian or nonagenarian or centenarian or 'old people' or eldest or oldest).ti,ab. or (individual adj2 (patient* or participant*) adj1 data*).ti,ab. (Breed ouderenfilter) (2868423)	
	16	14 and 15 (962)	
	17	((smoking adj3 cess*) or (terminat* adj2 study)).ti,ab. not Withholding Treatment/ (21648)	
	18	16 not 17 (835)	
	19	(meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (275153)	
	20	18 and 19 (14)	
	2	(randomized controlled trial/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or randomized controlled trial.pt. or random*.ti,ab. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (988355)	
	22	18 and 21 (284)	
	51	48 or 50 (335) – resultaten search starten met plaatjestremmers (preventive)	
	53	20 not 51 (11)	
	54	22 not 51 (257)	
	55	54 not 53 (251)	

Embase (Elsevier)	'cardiovascular disease'/exp/mj OR (myocard* NEAR/2 infarct*):ab,ti OR 'cerebral vascular accident':ab,ti OR stroke:ab,ti OR ((cerebrovascular OR cardiovascular OR heart OR vascular) NEAR/3 (disease* OR disorder* OR event*)):ab,ti AND ('antithrombocytic agent'/exp/mj OR dipyridamol:ab,ti OR clopidogrel:ab,ti OR prasugrel:ab,ti OR ticagrelor:ab,ti OR 'acetylsalicylic acid':ab,ti OR 'platelet aggregation inhibitors':ab,ti) AND ('aged'/exp OR 'geriatric assessment'/exp OR aged:ti OR elderly:ab,ti OR geriatric*:ab,ti OR 'community dwelling':ab,ti OR frail*:ab,ti OR ageing:ab,ti OR aging:ab,ti OR septuagenarian*:ab,ti OR octogenarian*:ab,ti OR nonagenarian*:ab,ti OR centenarian*:ab,ti OR 'old people':ab,ti OR eldest:ab,ti OR oldest:ab,ti OR (individual NEAR/2 (patient*i OR participant*) NEAR/2 data*):ab,ti) AND ((dutch)/lim OR (english)/lim) AND (embase)/lim AND ('treatment withdrawal'/exp OR cessation:ab,ti OR stop*:ab,ti OR termina*:ab,ti OR cease:ab,ti OR ceasing:ab,ti OR discontinua*:ab,ti OR withdrawal:ab,ti) NOT search starten met plaatjesremmers NOT ((smoking NEAR/3 cess*):ab,ti OR (terminat* NEAR/2 study):ab,ti NOT 'treatment withdrawal'/exp) AND 'meta analysis'/de OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp)) (4) 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti NOT 'conference abstract':it (176)	

Exclusietabel

Auteur en jaartal	Redenen van exclusie
Weimar, 2013	Deelnemers jonger dan 70 jaar

4 Evidencetabellen en kwaliteitsbeoordelingen

Onderstaand de evidencetabellen bij de noten bij de NHG-Standaard, voor zover deze niet uit de Europese richtlijn zijn overgenomen. Van noten die wel op de Europese richtlijn berusten zijn deze gegevens niet beschikbaar.
In de evidencetabellen zijn de gegevens uit de literatuur die gevonden is met de zoekstrategieën zoals beschreven in hoofdstuk 3 samengevat. Bij een deel van de noten is tevens de kwaliteit van de gevonden onderzoeken beoordeeld. Deze is dan eveneens samengevat in een tabel.

Noot 4: Coronaire-arteriële-calcium-score

Evidencetabel

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison/control (C)	Follow-up	Outcome measures and effect size	Comments
Peters, 2011 PS. Individuele studiekarakteristieken en resultaten zijn geëxtraheerd uit de SR, tenzij anders aangegeven	SR van cohort studies *Literatuur search op 7 sept 2011* **A**: Polonsky, 2010 **B**: Erbel, 2010 **C**: Elias-Smale, 2010 **D:** Mohlenkamp, 2011 <u>Study design</u>: SR <u>Setting and Country</u>: Nederland (SR) **A**: USA **B**: Duitsland **C**: Nederland **D:** Duitsland	Inclusiecriteria SR: - Studies naar de toegevoegde waarde van de CAC-score wanneer toegevoegd aan een model met traditionele risicofactoren - Uitkomstmaten: fatale and non-fatale CV-events - Domein: patiënten zonder symptomatische HVZ en zonder DM Exclusiecriteria SR: - Geen reclassificatie-maat gerapporteerd (toevoeging WdR) <u>Belangrijkste baseline karakteristieken van individuele studies</u>:	Interventie (toegevoegd aan risicopredictiemodel op basis van traditionele RF): **A**: Mean CACS **B**: ln (CACS +1) **C**: ln (CACS+1) **D**: Sum CACS	Controle: risicopredictie op basis van traditionele RF. Definitie intermediair risico: **A**: 3-10% AR; 5-jaars **B**: 10 tot 20% en 6 to 20% AR; 5 jaars **C**: 10 tot 20% AR; 10-jaars **D**: 3-10% AR; 5-jaars	<u>Follow-up (jaren)</u> **A**: 6 jr **B:** 5 jr **C**: 9 jr **D**: 5 jr <u>Incomplete data</u> Niet gerapporteerd <u>Event rate</u> **A**: 3,6% **B:** 2,3% **C**: 6,7% **D**: 2,2%	<u>Uitkomstmaten</u> **A**: fatale en niet-fatale coronaire hartziekten **B**: fatale en niet-fatale coronaire hartziekten **C:** fatale en niet-fatale coronaire hartziekten **D:** fatale en niet-fatale hart- en vaatziekten (CVD) <u>Effectmaten</u> **- Net Reclassification Index (BI) in %** **A**: - overall 25 (16 to 34) - intermediate 55 (41 to 69) **B***: intermediate risk 10-20%:* - overall 22 - intermediate 22 *intermediate risk 6-20%:* - overall 20 (6 to 33) - intermediate 31 **C**: - overall 14 (4 to 24)	Author's conclusion: 'The evidence for added value for CAC is considerable'. 'Although current guidelines on the use of imaging for asymptomatic atherosclerosis contain conflicting recommendations, the majority of guidelines point towards the usefulness of CAC in risk prediction for the development of cardiovascular events, especially in individuals that are classified at intermediate risk.' 'The present SR also showed that intermediate risk individuals may benefit most from additional assessment using CAC.' Personal remarks on study quality,

	Source of funding: Niet commercieel (deze SR); niet gerapporteerd per studie	N, leeftijd (gemiddeld in Jaren) **A**: 5868; 42 **B**: 4129; 59 **C**: 2028; 70 **D:** 1934; 57 *Geslacht:* **A**: 46% man **B**: 47% man **C**: 43% man **D:** 31% man				**D**: - overall 25 **- Δ C-statistic** **A**: 0,76 → 0,81: 0,05 **B:** 0,68 → 0,75: 0,07 **C**: 0,72 → 0,76: 0,04 **D**: 0,72 → 0,76: 0,04	conclusions, and other issues (potentially) relevant to the research question: - enige heterogeniteit van deze 4 studies met betrekking tot populatie, follow-up duur, definitie risicocategorieën, CAC drempelwaarden, eindpunten en opgenomen risicofactoren in het traditionele model; AMSTAR 5/11 Level of evidence: GRADE (per comparison and outcome measure) including reasons for down/upgrading. Uitkomst NRI: Laag, 1 level downgrading op basis van onderzoeksopzet en matig-lage AMSTAR score; 1 level downgrading o.b.v te weinig informatie over publicatiebias
Paixao, 2015	Meta-analyse NRI	Inclusiecriteria SR: - Studies naar de toegevoegde	Interventie (toegevoegd aan risicopredictiemode	Controle: risicopredictie op basis van traditionele RF.	Follow-up (jaren): **A**: 6 jr	Uitkomstmaten	Author's conclusion: 'In a young multi-ethnic cohort, the addition of

PS. Individuele studiekarakteristieken en resultaten zijn geëxtraheerd uit de SR, tenzij anders aangegeven	*Literatuur search tot en met 31 december 2014.* **A**: Polonsky, 2010 (MESA) **B**: Erbel, 2010 (HNR) **C**: Elias-Smale, 2010 (Rotterdam) **D:** Paixao, 2015 (DHS) <u>Study design</u>: Random-effects meta-analyse <u>Setting and Country</u>: Nederland (SR) **A**: USA **B**: Duitsland **C**: Nederland **D:** USA <u>Source of funding:</u>	waarde van de CAC-score wanneer toegevoegd aan een model met traditionele risicofactoren - Studies die een NRI rapporteerden <u>Belangrijkste baseline karakteristieken van individuele studies</u>: <u>N, leeftijd (gemiddeld in jaren)</u> **A**: 5868; 42 **B**: 4129; 59 **C**: 2028; 70 **D:** 2084; 44 <u>*Geslacht*</u>*:* **A**: 46% man **B**: 47% man **C**: 43% man **D:** 44% man	l op basis van traditionele RF): **A**: Mean CACS **B**: ln (CACS +1) **C**: ln (CACS +1) **D**: ln (CACS +1)	Definitie intermediair risico: **A**: 3 tot 10% AR; 5-jaars **B**: 10 tot 20% en 6 tot-20% AR; 5 jaars **C**: 10 tot 20% AR; 10-jaars **D**: 6 tot 20% AR; 10-jaars	**B:** 5 jr **C**: 9 jr **D**: 9 jr <u>Incomplete data</u> Niet gerapporteerd <u>Event rate</u> **A**: 3,6% **B:** 2,3% **C**: 6,7% **D**: 2,7% (57/2084)	**A**: fatale en niet-fatale coronaire hartziekten **B**: fatale en niet-fatale coronaire hartziekten **C:** fatale en niet-fatale coronaire hartziekten **D:** fatale en niet-fatale coronaire hartziekten <u>Effectmaten</u> **- Net Reclassification Index (BI) in %** **A**: - overall 25 (16 to 34) - intermediate 55 (41 tot 69) **B:** intermediate risk 10 tot 20% - overall 22 - intermediate 22 intermediate risk 6 tot 20% - overall 20 (6 tot 33) - intermediate 31 **C**: - overall 14 (4 tot 24) **D**: - overall 21 (4 tot 38) - **Pooled $NRI_{overall}$ A-D** 20,2% (BI 14,6–25,8); (I^2 0%; p = 0,451) **- Δ C-statistic** **A**: 0,76 → 0,81: 0,05 **B:** 0,68 → 0,75: 0,07 **C**: 0,72 → 0,76: 0,04	CAC to a model composed of traditional CHD risk factors significantly improved discrimination and risk classification' Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question: - alleen coronaire hartziekten, iets verschillende definities uitkomstmaat; I^2 underpowered?, AMSTAR 2/11 score (= zeer laag) Level of evidence: GRADE (per comparison and outcome measure) including reasons for down/upgrading. Uitkomst NRI: Laag, 1 level downgrading op basis van onderzoeksopzet en matig-lage AMSTAR score; 1 level downgrading o.b.v te

	Niet commercieel (deze SR); niet gerapporteerd per studie					**D**: 0,86 → 0,89 : 0,03	weinig informatie over publicatiebias

Noot 5: Body mass index

Evidencetabel

Study reference	Study characteristic	Patient characteristics	Prognostic factor(s)	Follow-up	Outcome measures and effect size	Comments
Wormser, 2011	Type of study: cohort study Setting: Emerging Risk Factors Collaboration using records from 58 prospective cohort studies Country: 17 countries Source of funding: Non-commercial (British Heart Foundation and UK Medical Research Council)	Inclusion criteria: • Concomitant information at baseline for weight, height, waist and hip circumference • Cause-specific mortality or vascular morbidity • ≥ 1 yr follow-up Exclusion criteria: - Having previous vascular disease N = 221.934 individual records Mean age ± SD: 58 ± 9 Sex: 44% M / 56% F	BMI Also: waist circumference and waist-to-hip ratio	Endpoint of follow-up: 10 yr For how many participants were no complete outcome data available? All participants had ≥ 1 yr follow-up, as it was a selection criterium. 9355 participants excluded from analysis, with BMI ≤ 20 kg/m^2	<u>Cardiovascular disease (10 yr)</u> HR (95%-CI): 1,23 (1,17 to 1,29) Adjusted HR (95%-CI)*: 1,07 (1,03 to 1,11) C-index change (95%-CI): -0,0001 (-0,0005 to 0,0002), P = 0,430 Net reclassification improvement (95%-CI): -0,19% (-0,70 to 0,32), P = 0,461	* Adjusted for age, sex, smoking, systolic blood pressure, history of diabetes and total and HDL cholesterol
Van Dis, 2012	Type of study: cohort study Setting: Monitoring Project on Chronic Disease Risk	Inclusion criteria: • Concomitant information at baseline for weight, height, waist and hip circumference	Obesity = BMI ≥ 30 kg/m^2 Also: maternal myocardial infarction (MI)	Endpoint of follow-up: 10 yr For how many participants were no	<u>NRI</u> **Risk categories 0-5%, 5-10%, ≥ 10%** CRF + obesity - Men: 2,2%; P = 0,3	NRI = Net Reclassification Index CRF = Classical risk factors

	Factors (MORGEN), 1993-1997 Country: The Netherlands Source of funding: Non-commercial (Netherlands Heart Foundation)	• Cause-specific mortality or vascular morbidity • ≥ 1 yr follow-up Exclusion criteria: • < 35 yr • Without informed consent • Without successful record linkage • Prevalent cases of MI, stroke or heart failure N = 12.818 individual records Mean age ± SD: 48,0 ± 7,4 in men; 48,9 ± 7,4 in women Sex: 47% M / 53% F	Classical risk factors (CRF) model	complete outcome data available? 11 (0,09%)	- Women: 1,1%; P = 0,7 **Risk categories 0-10%, 10-20%, ≥ 20%** CRF + obesity - Men: 3,8%; P = 0,05 - Women: 2,7%; P = 0,2	

Table of quality assessment – prognostic studies

(The criteria used in this checklist are adapted from: Altman DG (2001). Systematic reviews of evaluations of prognostic variables. In: Egger M, Smith GD, Altman DG (eds.). Systematic reviews in health care. London: BMJ Books; Laupacis A, Wells G, Richardson WS, Tugwell P (1994). Users' guides to the medical literature. How to use an article about prognosis. Evidence-Based Medicine Working Group. JAMA,272:234-7)

Study reference (first author, year of publication)	**Was there a representative and well-defined sample of patients at a similar point in the course of the disease?** (yes/no/unclear)	**Was follow-up sufficiently long and complete?** (yes/no/unclear)	**Was the outcome of interest defined and adequately measured?** (yes/no/unclear)	**Was the prognostic factor of interest defined and adequately measured?** (yes/no/unclear)	**Was loss to follow-up / incomplete outcome data described and acceptable?** (yes/no/unclear)	**Was there statistical adjustment for all important prognostic factors?** (yes/no/unclear)	**Level of evidence**
Wormser, 2011	No (unequal start)	Yes	Yes	Yes	Unclear	Yes	A2

Van Dis, 2012	Yes	Yes	Yes	Yes	Yes	Yes	A2

Noot 6: Elektrocardiografie

Evidence-tabel

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Outcome measures and effect size	Comments
Shah, 2016	Type of study: NHANES–I (derivation cohort) NHANES–III (validation cohort) Setting and Country: US civilian non-institutionalised Source of funding: non-commercial	Inclusion criteria: - leeftijd 40 tot 74 jaar - blanco cardiale voorgeschiedenis Exclusion criteria: N = individual records N = 9969 (NHANES I: N = 4192; NHANES-III: N = 6418) Mean age: 55,3 jaar (SD 10,1) Sex: M 47,3%	Ecg-afwijking Definitie CV events Op basis van ICD codering. MACE = incident nonfatal or fatal CVD outcomes Beoordeling ECG: 12-lead ECG, gecodeerd met NOVACODE ECG programma Definitie ECG afwijking: Op basis van Minnesota codes, Cardiac Infaction injury Score en ECG simple score	Follow-up median 18,8 (IQR 12,4-20,1) Missende data 6% Aantal CV events: 2,8%	**Cardiovasculaire mortaliteit** c-statistics 0,82 (95%-BI 0,80 tot 0,85); Δ 0,01 verbetering NRI 11% (95%-BI 7 tot 4%)*	*Berekend in nieuwe risicopredictiemodel met Framingham risicoscore en ecg-variabelen Methodologische tekortkomingen: • Doodsoorzaken op basis van overlijdensaktes • Medische voorgeschiedenis en rookstatus mogelijk onbetrouwbaar • Ecg's niet in alle centra beschikbaar • Beoordeling ecg's alleen door programma
Auer, 2012	Type of study: Population based cohort (Health ABC)	Inclusion criteria: Leeftijd 70 tot 79 jaar Exclusion criteria:	Ecg-afwijking Definitie CV events acuut MI, coronaire mortaliteit, opname voor angina of	Mediane follow-up 8,2 jaar (range 9-10,2)	**Cardiovasculaire morbiditeit en mortaliteit** HR 1,63 (95%-BI 1,31 tot 2,02)* NRI 7,4% (95%-BI 3,1 tot 19,0%)	* Gecorrigeerd voor leeftijd, geslacht, totaal cholesterol, HDL, syst RR, roken, DM, ras, opleiding, omgeving, LDL, kreatinine, alcohol, lichamelijke

	<u>Setting and Country</u>: US <u>Source of funding:</u> non-commercial	N = individual records N = 2168 Mean age: 73,5 jaar (SD 7,8) Sex: M 45% Race: 41% black	revascularisatie (op basis van anamnese, patientendossiers, beoordeling door geblindeerde clinici) <u>Beoordeling ecg:</u> 12-lead ecg, gecodeerd volgens de Minnesota Code Classification system, beoordeeld door 2 reviewers (bij verschil van inzicht een senior) <u>Definitie ecg-afwijking:</u> <u>Major:</u> • Q-QS • LVH • WPW syndroom • complete bundeltak- of intraventriculaire block • boezemfibrilleren, of –flutter • grote ST-T-veranderingen <u>Minor:</u> • geringe ST-T-veranderingen Definitie intermediaire groep: tienjaarsrisico van 10-20 %	Missende data 1% Aantal CV events: 16% Totale sterfte: 27%	NRI (intermediaire risicogroep) 6,7% (95%-BI 1,2 tot 19,3%) (gecorrigeerd voor vertekening) NB Geen verschil tussen major en minor ecg-aafwijkingen	activiteit, statinegebruik, ACE-remmers, oestrogeengebruik. Methodologische tekortkomingen: • Relatief korte follow-up (median < 10 jaar) • Hoge leeftijd van deelnemers
Jörgensen, 2014#	<u>Type of study:</u> Copenhagen City Heart Study, prospectief cohort <u>Setting and Country</u>: Denemarken	Inclusie criteria: Leeftijd ≥ 65 jaar Exclusie criteria: Niet gegeven N = individual records	Ecg-afwijking <u>Definitie CV events</u> Op basis van ICD-codering <u>Beoordeling ecg:</u> 12-lead ecg, gecodeerd volgens de Minnesota Code Classification	Mediane follow-up 9,8- 11,9 jaar For how many participants were no complete outcome data available? geen	**<u>Cardiovasculaire morbiditeit en mortaliteit</u>** **I. Ecg** HR 1,35 (95%-BI 1,24 tot 1,47)* NRI 4,2% (95%-BI 3,5 tot 5,6) C-statistics 0,66 (Δ 0,009)	*Gecorrigeerd voor Framingham Global Risk score # gecorrigeerd voor European Heart Score

	Source of funding: non-commercial	N = 6991 Gemiddelde leeftijd: Zonder ecg-afw 69,5 ± 3,5 Met ecg-afw 70,2 ± 4,1 Geslacht: Zonder ecg-afw 39% M Met ecg-afw 46% M	system, beoordeeld door 2 reviewers (bij verschil van inzicht een 3e) Definitie ecg-afwijking: • Q golf • ST depressive • T golfafwijking • Linker ventrikel geleidingsdefect (major) • LVH (major)	Aantal CV events (fataal en niet-fataal): 55% Aantal ecg-afwijkingen: 30,6%	**II.Linkerventrikelhypertrofie** HR 1.32 (95%-BI 1,21 tot 1,45) NRI **Cardiovasculaire mortaliteit** **I. Ecg** HR 1,51 (95%-BI 1,38 tot 1,65)# NRI 7,1% (95%-BI 6,7 tot 9%) C-statistics 0,72 (Δ 0,014) **II. Linkerventrikelhypertrofie** HR 1,47 (95%-BI 1,31 tot 1,65) NRI 2,7% (95%-BI 1,0 tot 4,4)	
Graversen, 2016#	Type of study: Copenhagen City Heart Study Setting and Country: Denemarken Source of funding: non-commercial	Inclusiecriteria: Leeftijd 21 tot 79 jaar Exclusiecriteria: DM N = individual records N = 8476 Mediane leeftijd: 55 jaar Sex:	Ecg-afwijkingen Definitie CV events Op basis van ICD-codering Beoordeling ecg: 12-lead ecg, gecodeerd volgens de Minnesota Code Classification system, beoordeeld door 2 reviewers (bij verschil van inzicht een senior) Definitie ecg-afwijking: Major: • Q-QS	Mediane follow-up 18 jaar CV events 7,8% Missende data 7,7%	**Cardiovasculaire mortaliteit** Major ecg-afwijkingen HR 1,47 (95%-BI 1,22 tot 1,78)* NRI 1,9% (BI niet gegeven, p = 0,540) ΔAUC 0,004 (-0,001-0,009) (p = 0,086) Minor ecg-afwijkingen HR 1,01 (95%-BI 0,72 tot 1,43)* Subgroep intermediair risico en leeftijd 40 tot 70 jaar	* Gecorrigeerd voor leeftijd, geslacht, syst RR, rookstatus, taotal cholesterol; risicopredictiemodel: SCORE.

		42% M	• LVH • WPW syndroom • complete bundeltak- of intraventriculaire block • boezemfibrilleren, of –flutter • grote ST-T veranderingen <u>Minor:</u> • geringe ST-T veranderingen		Major ecg-aafwijkingen NRI 6,7% (BI niet gegeven, p = 0,370)	
Desai, 2014	<u>Multi-Ethnic study of Aterosclerosis (MESA) cohort</u> <u>Setting and Country</u>: US <u>Source of funding:</u> non-commercial	Inclusiecriteria: Leeftijd 45 tot 84 jaar Exclusiecriteria: N = individual records N = 6406 Mediane leeftijd Zonder ecg-afw 61 ± 10 Met ecg-afw 65 ± 10 Geslacht: Zonder ecg-afw 46% M Met ecg-afw 43% M Ras: Zonder ecg-afw 39% blank 26% negroïde	Ecg-afwijkingen Definitie CV events CHD included nonfatal myocardial infarction, death due to CHD, and hospitalized angina <u>Beoordeling ecg:</u> 12-lead ecg, gecodeerd volgens de Minnesota Code Classification system, beoordeeld op kwaliteit en fouten <u>Definitie ecg-aafwijking:</u> <u>Major:</u> • Q-QS • LVH • WPW syndroom • complete bundeltak- of intraventriculaire block • boezemfibrilleren, of -flutter • grote ST-T veranderingen <u>Minor:</u> • geringe ST-T veranderingen	Mediane follow-up 10 jaar CV events 6,3% Missende data 5,2%	**<u>Coronaire morbiditeit</u>** Major ecg-afwijkingen HR 1,83 (95%-BI 1,30 tot 2,58)* Minor ecg-afwijkingen HR 1,38 (95%-BI 1,04 tot 1,83)* NRI 2% (BI niet gegeven) **<u>Coronaire morbiditeit en mortaliteit</u>** NRI 5% (p = 0,02) C-statistics 0,736 (Δ 0,009; p = 0,02) **<u>Coronaire mortaliteit</u>** Major ecg-afwijkingen HR 1,55 (95%-BI 0,72 tot 3,37)* Minor ecg-afwijkingen HR 2,42 (95%-BI 1,44 tot 4,09)* NRI 9% (BI niet gegeven)	* Gecorrigeerd voor leeftijd, ras, geslacht, systolische RR, total cholesterol, HDL, DM, roken en antihypertensiva

		13% Chinees 22% Spaans Met ecg-aafw 32% blank 33% negroïde 10% Chinees 25% Spaans				

 # Graversen (2016) en Jorgensen (2014) maken gebruik van hetzelfde cohort maar hanteerden verschillende inclusiecriteria voor leeftijd.

Table of quality assessment – prognostic studies

Study reference (first author, year of publication)	Was there a representative and well-defined sample of patients at a similar point in the course of the disease? (yes/no/unclear)	Was follow-up sufficiently long and complete? (yes/no/unclear)	Was the outcome of interest defined and adequately measured? (yes/no/unclear)	Was the prognostic factor of interest defined and adequately measured? (yes/no/unclear)	Was loss to follow-up / incomplete outcome data described and acceptable? (yes/no/unclear)	Was there statistical adjustment for all important prognostic factors? (yes/no/unclear)	Level of evidence
Shah, 2016	Yes	Yes	Yes	Yes	Yes	Yes	A2
Auer, 2012	Yes	No	Yes	Yes	Yes	Yes	B
Jorgensen, 2014	Yes	Yes	Yes	Yes	Yes	Yes	A2
Graversen, 2016	Yes	Yes	Yes	Yes	Yes	Yes	A2
Desai, 2014	Yes	Yes	Yes	Yes	Yes	Yes	A2

Noot 7: Enkel-armindex

Evidencetabellen

A: Evidencetabel voor systematische reviews van RCT's en observationele onderzoeken (prognose-onderzoeken)

Referentie onderzoek	Onderzoeks-karakteristieken	Patiënt karakteristieken	Prognostische factor	Follow-up	Uitkomstmaten en mate van effect	Opmerkingen
Lin, 2013	Systematische review van cohorten *Literatuur search van 1996 tot september 2012* Cohorten (alleen met NRI als uitkomstmaat) **A**: Rotterdam study (Kavousi, 2012) **B**: Health ABC (Rodondi, 2010) **C**:ARIC study (Murphy, 2012) **D**: MESA cohort (Yeboah, 2012) Setting and Country: USA (SR) **A**: Europa **B**: USA **C:** USA **D:** USA	Inclusiecriteria: - prospectieve cohortonderzoeken alle Framingham Risico Score (FRS) voorspellers (ATP-III): leeftijd, geslacht, rookstatus, systolische bloeddruk, totaal cholesterol en HDL - uitkomstmaten: cardiovasculaire morbiditeit en mortaliteit - min. follow-up 3 mnd - Engelstalig - domein: patiënten zonder HVZ, DM of ernstige chronische nierziekten	Interventie (toegevoegd aan risicopredictiemodel op basis van traditionele RF): **A**: EAI **B**: EAI **C:** EAI **D**: EAI Risicopredictiemodel: A tot en met B: Framingham Risk Score Referentiegroep ABI: **A:** 0,91- 1,40 **B:** 1,01-1,30 **C:** 1 SD **D:** 1 SD Definitie intermediair risico: **A**: 10 tot 20% AR: 10 jaar	Follow-up (jaren): **A**: 7 **B:** 10 **C:** 14 **D:** 8 Incomplete data: Niet gerapporteerd Event rate: **A:** 5,8% **B**: 16% **C:** 5,6% **D:** NR	Uitkomstmaten **A**: coronaire morbiditeit en mortaliteit **B:** coronaire morbiditeit en mortaliteit **C:** cardiovasculaire morbiditeit en mortaliteit **D:** cardiovasculaire morbiditeit **NRI in totale groep** **A:** 0,6% (95%-BI -1,8 to 2,9%) **B:** coronaire morbiditeit en mortaliteit*:* 3% (95%-BI 0,04 to 6,5) coronaire mortaliteit: 7,9% (95%-BI NR) **C:** 0,8% (95%-BI NR, p = 0,5) **D:** niet beschreven	Conclusies auteurs: "Despite the accrual of new evidence, we found limited evidence to support the added value of the ABI in current CAD or CVD risk prediction, as well as limited trial evidence for treatment of CVD in persons with asymptomatic or minimally symptomatic PAD." Persoonlijke kanttekeningen over de kwaliteit van het onderzoek, conclusies en andere problemen relevant voor de onderzoeksvraag: Goede vergelijking van NRI tussen de cohorten wordt belemmerd door gebruik van verschillende uitkomstmaten (coronaire versus cardiovasculaire morbiditeit en mortaliteit) en verschillende definities van risicocategorieën. De kwaliteit van de SR was goed (AMSTAR 9/11). Niveau van bewijs: GRADE (per vergelijking en uitkomstmaat

	Source of funding: Agency for Healthcare Research and Quality; niet gerapporteerd per studie	Belangrijkste baselinekarakteristieken: N, leeftijd (gemiddeld in jaren) **A**: 5933; 69 **B**: 2191;74 **C:** 11594; 54 **D:** 1330; 64 *Geslacht:* **A**: 59% vrouw **B**: 55% vrouw **C:** 56% vrouw **D:** 33% vrouw	**B**: 10 tot 20% AR; 7,5 jaar **C:** 6 tot 19%; 10 jaar **D:** 3 tot 21% AR; 7,5 jaar		**NRI in intermediaire groep** **A:** 3,8% (95%-BI -2,9 to 10,5%) (gecorrigeerd) **B:** coronaire morbiditeit en mortaliteit: 19,3% (95%-BI NR) (niet gecorrigeerd)* **C:** niet beschreven **D**: 6,8% (95%-BI NR) (niet gecorrigeerd)*	inclusief reden voor verlaging of verhoging) Bij de uitkomstmaten NRI (totale en intermediaire groep) zijn de aanvullende onderzoeken meegenomen in het bepalen van het niveau van bewijs (zie hoofdtekst). * NRI-berekeningen voor intermediaire risicosubgroepen zonder correctie voor vertekening zijn altijd hoger dan de gecorrigeerde NRI's en zijn waarschijnlijk overschattingen. (Cook, 2011)
Fowkes, 2014	Meta-analyse ABI Collaboration, 18 cohorten Setting and Country: USA, Europa, Australie Source of funding: Niet commercieel; niet gerapporteerd per studie	Inclusiecriteria: - Framingham Risico Score (FRS) voorspellers (ATP-III): leeftijd, geslacht, rookstatus, systolische bloeddruk, totaal cholesterol en HDL - diabetes indicator - etniciteit (alleen blank) - onderzoek locatie - EAI Exclusiecriteria:	Interventie (toegevoegd aan risicopredictiemodel op basis van traditionele RF): - EAI Risicopredictiemodel: Framingham Risk Score Referentiegroep ABI: 1,11-1,40 Definitie intermediair risico:	Follow-up (jaren): 5-20 jr Incomplete data 7,4% van de data van mannen en 2,9% van vrouwen Event rate: 12,6%	Uitkomstmaten: Coronaire morbiditeit en mortaliteit: **NRI totale groep** 4,3% (95%-BI 0,0 to 7,6%) bij mannen en 9,6% (95%-BI 6,1 to 16,4%) bij vrouwen **NRI in nieuw predictiemodel (met ABI):** 2,0% (95%-BI 2,3 tot 4,2%) bij mannen en	Conclusies auteurs: "The results of our study provide some support for the use of an ABI risk model especially in individuals at intermediate risk and when performance of the base risk factor model is modest. Furthermore, if physicians are uncertain about how well the FRS performs in their practice, using the ABI model is likely to compensate for any deficiencies in the FRS." Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question:

		- niet- blanke populatie - niet-valide EAI - coronaire hartziekten <u>Belangrijkste baseline karakteristieken</u>: <u>N, leeftijd (gemiddeld in jaren):</u> 44752; NR (62 uit Fowkes, 2008) <u>*Geslacht*</u>*:* *46% vrouw*	Coronaire morbiditeit en mortaliteit: 10 tot 19% AR; 10-jaars cardiovasulaire mortaliteit: 2 tot 4% AR; 10-jaars		1,1% (95%-BI 1,9 tot 0,1%) bij vrouwen **Δ C-statistics** Mannen: 0,672 -> 0,685: 0,013 Vrouwen: 0,578-> 0,690:0,112 **NRI intermediaire groep** Mannen: 15,9% (95%-BI 6,1 tot 20,6%) (niet gecorrigeerd) Vrouwen: 23,3% (95%-BI 13,8 tot 62,5%) (niet gecorrigeerd) <u>Cardiovasulaire mortaliteit:</u> **NRI totale groep** 5,7% (95%-BI 2,7 tot 7,9%) bij mannen en 15,7% (95%-BI 11,3 tot 20,2%) bij vrouwen **Δ C-statistics** Mannen: 0,684 -> 0,710: 0,026 Vrouwen: 0,449-> 0,652: 0,203	Het effect van de ABI is waarschijnlijk geen onafhankelijke risicofactor maar afhankelijk van de prestatie van de risicoscore. Niveau van bewijs: GRADE (per vergelijking en uitkomstmaat inclusief reden voor verlaging of verhoging) Bij de uitkomstmaten NRI (totale en intermediaire groep) zijn de aanvullende onderzoeken meegenomen in het bepalen van het niveau van bewijs (zie hoofdtekst). * NRI-berekeningen voor intermediaire risicosubgroepen zonder correctie voor vertekening zijn altijd hoger dan de gecorrigeerde NRI's en zijn waarschijnlijk overschattingen. (Cook, 2011)

					NRI intermediaire groep Mannen: 20,2% (95%-BI 11,6 tot 22,5%) (niet gecorrigeerd)* Vrouwen: 18,0% (95%-BI 13,1 tot 18,0%) (niet gecorrigeerd)*	

B: Evidencetabel voor RCT's en observationele onderzoeken (prognose-onderzoeken) na publicaties van de SR

Referentie onderzoek	Onderzoekskarakteristieken	Patiënt karakteristieken	Prognostische factor	Follow-up	Uitkomstmaten en mate van effect	Comments
Yeboah, 2016	Soort onderzoek: prospectief cohortonderzoek (MESA cohort) Setting: population-based Countries: USA Source of funding: non-commercial	Inclusiecriteria: - personen zonder HVZ - leeftijd 40 tot 75 jaar Exclusie: EAI ≥ 1,4 Belangrijkste baseline karakteristieken: N = 6,814 Gemiddelde leeftijd: 61,2 jaar Geslacht: 53% vrouw	Interventie (toegevoegd aan risicopredictiemodel op basis van traditionele RF): EAI Risicopredictiemodel: Framingham Risk Score Referentiegroep ABI: Per 0,11 SD Definitie intermediair risico: 10 tot 20% AR; 10-jaars	Gemiddelde follow-up: 10 jaar Incomplete data 23,9% incomplete data, statine gebruik of EAI ≥ 1,4 Event rate: 194 (3,7%)	Cardiovasculaire morbiditeit en mortaliteit **NRI totale groep** 3,9% (95%-BI -1,1 to 10,9) AUC 0,78 (Δ 0,04)	Het MESA cohort (vroeger en kleiner cohort) maakte ook deel uit van de systematische review van Lin et al. (2013).
Velescu, 2015	Soort onderzoek: cohortonderzoek Setting: population-based	Inclusiecriteria: • leeftijd 35-74 jaar • valide ABI • zonder HVZ	Interventie (toegevoegd aan risicopredictiemodel op basis van traditionele RF): EAI	Gemiddelde follow-up: 10 jaar Incomplete data	Cardiovasculaire morbiditeit en mortaliteit	

	Countries: Spanje Source of funding: Non-commercial	Exclusiecriteria: • korter dan 6 mnd woonachtig in onderzoeksgebied • wonen binnen instelling • terminale ziekte • EAI > 1,39 N = 5248 Gemiddelde leeftijd: 53,7 jaar Geslacht: 46% man	Risicopredictiemodel: Framingham-REGIGOR score (Framingham Risk Score geüpdatet met Spaanse data) Referentiegroep ABI: ABI ≤ 0,9 Definitie intermediair risico: 5-10% AR; 10-jaars	24 (0,4%) incomplete data Event rate: 590	**NRI totale groep** 2,9% (95%-BI 1,4 to 4,5%) Δ C-statistics 0,787 -> 0,795 (0,008) **NRI intermediaire groep** 5,1% (95%-BI 1,5 to 10,6%) (niet gecorrigeerd)	
Ferket, 2014	Soort onderzoek: twee cohorten (NHANES en subset van Rotterdam study) Setting: population-based Countries: USA, Nederland Source of funding: Non-commercial (Netherlands Organisation for Health Research and Development)	Karakteristieken per cohort: NHANES/Rotterdam Inclusiecriteria: 40 jaar en ouder/55 jaar en ouder Exclusiecriteria: - N = 3736/1915 Gemiddelde leeftijd: 53/70 Geslacht: 48%/45% man	Interventie (toegevoegd aan risicopredictiemodel op basis van traditionele RF): EAI Risicopredictiemodel: Framingham Risk Score Referentiegroep ABI: ABI ≤ 0,9 Definitie intermediair risico: 10-20% AR; 10-jaars Definitie cardiovasulaire ziekten: hartinfarct, coronaire dood en ischemisch herseninfarct	Gemiddelde follow-up: NHANES 30 jaar Rotterdam study 7 jaar Incomplete data Niet beschreven Event-rate: NR	Cardiovasulaire morbiditeit **NRI totale groep** 0,0% (95%-BI -3,0–3,0%) Δ c-statistics tov FRS 0,00 (95%-BI 0,00-0,00)	De Rotterdam study maakte deel uit van de systematische review van Lin et al. (2013).

Table of quality assessment – prognostic studies

Study reference (first author, year of publication)	Was there a representative and well-defined sample of patients at a similar point in the course of the disease? (yes/no/unclear)	Was follow-up sufficiently long and complete? (yes/no/unclear)	Was the outcome of interest defined and adequately measured? (yes/no/unclear)	Was the prognostic factor of interest defined and adequately measured? (yes/no/unclear)	Was loss to follow-up / incomplete outcome data described and acceptable? (yes/no/unclear)	Was there statistical adjustment for all important prognostic factors? (yes/no/unclear)	Level of evidence
Yeboah, 2016	Yes	Yes	Yes	Yes	No (not acceptable)	Yes	B
Velescu, 2015	Yes	Yes	Yes	Yes	Yes	Yes	A2
Ferket, 2014	Yes	Yes	Yes	Yes	Unclear	Yes	B

Noot 8: Etniciteit

Evidencetabellen

Study reference	**Study characteristics**	**Patient characteristics**	**Prognostic factor(s)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Gijsberts, 2015	Type of study: participant meta-analysis Setting: 15 population based cohorts worldwide Countries: USA, Germany, Japan, UK, Canada, NLD, Finland, Sweden, Norway Source of funding: Non-commercial (Netherlands Organisation for Health	Inclusion criteria: • Cohorts with available baseline data on age, sex, blood pressure, cholesterol fractions, smoking status, use of antihypertensive medication, diabetes mellitus and CIMT-measurements, follow-up information on occurrence of cardiovascular events • individuals to whom the Framingham criteria are applicable Exclusion criteria: • Cohorts without information about ethnicity if it was reasonable to assume that > 95% of the participants belonged to one race/ethnic group N = 60.211 individual records	Ethnicity: • White as reference group • Black • Asian • Hispanic	Mean follow-up: 9,1 yr (range 3,8 to 13,1 yr) For how many participants were no complete outcome data available? Incomplete data on mean common CIMT, cardiovascular risk factors, and (time to) CV events, approximately 12% of total values, were imputed	<u>Cardiovascular events</u> 10-yr event rate • White: 8,1% • Black: 9,2% • Asian: 6,7% • Hispanic: 7,8% • Total: 8,2% HR (95%-CI) **Age** • White 1,89 (1,86 to 1,93) reference	

	Research and Development)	Mean age: 59 yr Sex: 51% M / 49% F 46,788 Whites (78%) 7,200 Blacks (12%) 3,816 Asians (6%) 2,407 Hispanics (4%)			• Black: 1,52 (1,44 to 1,60), P < 0,05 • Asian: 1,75 (1,49 to 2,01) • Hispanic: 1,69 (1,48 to 1,90) **Total cholesterol** • White 1,09 (1,07 to 1,12) reference • Black: 1,20 (1,13 to 1,26), P < 0,05 • Asian: 0,95 (0,78 to 1,13) • Hispanic: 1,15 (0,96 to 1,34)	
Drawz, 2012	Type of study: cohort study Setting: 19.811 subjects of ALLHAT cohort Countries: USA Source of funding: Non-commercial funding. ALLHAT investigators received financial support by industry.	Inclusion criteria: • Age ≥ 55 yr • Hypertension with ≥ 1 additional risk factor for CHD Exclusion criteria: • Age > 74 • Missing baseline data for HDL, or both cLDL and total cholesterol • History of CHD (assessed with questionnaire) N = 19.811 Mean age: 64 yr	Ethnicity: • White • Black	5-yr follow-up For how many participants were no complete outcome data available? Not reported	<u>Coronary heart disease (CHD), 5-yr*</u> *Net Reclassification Improvement* Non-black, men: 1,3% (P = 0,54) Non-black, women: -5,5% (P = 0,11) Black, men: -4,1% (P = 0,46)	* NRI of model included CKD and race compared to basic model without these variables

		Sex: 51% M / 49% F 8108 Whites (61%) 5099 Blacks (39%)			Black, women: 4,4% (P = 0,31)	

Table of quality assessment – prognostic studies

Study reference (first author, year of publication)	**Was there a representative and well-defined sample of patients at a similar point in the course of the disease?** (yes/no/unclear)	**Was follow-up sufficiently long and complete?** (yes/no/unclear)	**Was the outcome of interest defined and adequately measured?** (yes/no/unclear)	**Was the prognostic factor of interest defined and adequately measured?** (yes/no/unclear)	**Was loss to follow-up / incomplete outcome data described and acceptable?** (yes/no/unclear)	**Was there statistical adjustment for all important prognostic factors?** (yes/no/unclear)	**Level of evidence**
Gijsberts, 2015	Yes	Yes	Unclear	Unclear	Yes	Yes	A2
Drawz, 2012	Yes	No (5 yr follow-up)	Yes	No (self-reported and Hispanic eligible in both black or non-black)	No (not described)	Yes	B

Noot 9: Urinezuur

Evidencetabellen

Study reference	**Study characteristics**	**Patient characteristics [2]**	**Intervention (I)**	**Comparison / control (C) [3]**	**Follow-up**	**Outcome measures and effect size [4]**	**Comments**
CVD morbidity and mortality							
Kavousi, 2012	Type of study: cohort study	Inclusion criteria: • Aged 55 and above • Living in or migrating to the research area	Uric acid levels	Risk model: Framingham Risk score	Length of follow-up:	Outcome measure-1 Defined as morbidity and	NRI specifies the amount of correct reclassification of estimated (not actual) events and non-events to 10 years. The NRI estimates were based on the

	Setting: Persons aged 55 years or older living in Rotterdam (The Rotterdam Study) Country: The Netherlands Source of funding: Non-commercial	Exclusion criteria: • Participants with a history of CHD (defined as clinically manifest myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty) N total at baseline: 5933 Important prognostic factors[2]: Age, mean (SD): 69 (9) Sex: 31% M Uric acid levels, median (25th, 75th percentile): 300,0 µmol/l (260,0, 360,0)	Risk model: Framingham Risk score		Median follow-up of 6,8 years Incomplete outcome data: 20 (0,3%) participants were lost to follow-up.	mortality due to CVD NRI (95%-CI) for total population, % Uric acid: 0,8 (-0,5 to 2,1) NRI (95%-CI) for Framingham Intermediate-Risk group, % Uric acid: 2,6 (1,0 to 4,2)	reclassification tables classifying participants in 10-year CHD risk categories of low (< 10%), intermediate (10% to 20%), and high (> 20%). Although not specifically stated, uric acid levels were most likely add continuously to the model to calculate the NRI.

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures.**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders).**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls.**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders.**

Study reference (first author, year of publication)	Bias due to a non-representative or ill-defined sample of patients?[1] (unlikely/likely/unclear)	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?[2] (unlikely/likely/unclear)	Bias due to ill-defined or inadequately measured outcome?[3] (unlikely/likely/unclear)	Bias due to inadequate adjustment for all important prognostic factors?[4] (unlikely/likely/unclear)
CHD morbidity and mortality				
Kavousi, 2012	Unlikely	Likely, median follow-up was 6,8 years	Unclear. Information was obtained on study outcomes from general practitioners and from letters and discharge reports from medical specialists. Events were classified by study physicians. However, it was unclear whether these results were validated.	Unlikely. Important risk factors were adequately used in the analyse.

1. **Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.**
2. **2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The Risk of Bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.**
3. **Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.**

Noot 10: Artitis psoriatica

Evidencetabellen

Study reference	Study characteristics	Patient characteristics [2]	Exposure (E)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Ogdie, 2015	Type of study: Cohort study Setting: Primary care medical record database (The Health	Inclusion criteria: • Patiënt with PsA, psoriasis or RA • Aged between 18 to 89 years • Obervation time in database after specific software implementation	PsA PsA were defined by the presence of at least one READ code consistent with these diseases (READ codes are	Unexposed controls Up to 10 unexposed controls from the general population without PsA, psoriasis, RA, or disease-modifying antirheumatic drugs (DMARD) prescriptions were randomly selected for each	Length of follow-up: Not reported Loss-to-follow-up:	1. CVD morbidity Defined by READ codes, HR (95%-CI) DMARD+: 1,17 (0,95 to 1,46) DMARD-: 1,24 (1,03 to 1,49) Adjusted for age, sex, hypertension, diabetes, hyperlipidaemia, smoking	

	Improvement Network (THIN)) Country: UK Source of funding: Non-commercial	<u>Exclusion criteria</u>: • Died or transferred out of the practice before specific software implementation <u>N total at baseline</u>: Exposure: 8706 Control: 81573 <u>Important prognostic factors</u>[2]: Characteristics for PsA patients were reported by use of disease-modifying anti-rheumatic drugs (DMARD). age ± SD: I: DMARD+: 49 (14) DMARD-: 51 (18) C: 49 (18) Sex: I: DMARD+: 51% M DMARD-: 51% M C: 45% M	standard medical diagnosis codes used in the UK general practice system)	patient with PsA and were matched on practice and index date within the practice (defined as latest of registration with the practice and diagnosis date).	Not reported <u>Incomplete outcome data</u>: Not reported	status (never, past, current) and start year in the cohort. 2. CVD mortality Defined by RAD codes based on UK ICD9 codes. Text comments in the database reporting the patient's death as CV were also used to classify CV death DMARD+: 0.96 (0.64 to 1.43) DMARD-: 1.07 (0.79 to 1.44) Adjusted for age, sex, hypertension, diabetes, hyperlipidaemia, smoking status (never, past, current) and start year in the cohort.	
Li, 2012	Type of study: Cohort study	<u>N total at baseline</u>: Unclear	PsA	No PsA	<u>Length of follow-up</u>:	1. Nonfatal CVD Not clearly stated what was defined as CVD, cases (PYs)	

	Setting: Registered nurses Country: USA Source of funding: Non-commercial	Important prognostic factors:[2] Not reported for patiënten with PsA			Total of 1709069 person-years Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	E: 10 (4213) C: 688 (1677052) HR 3,47 (95%-CI: 1,85 to 6,51) Adjusted for age, BMI, Smoking status, alcohol intake physical activity, race, family history of stroke/myocardial infarction, hypertension, hypercholesterolaemia, current aspirin use, multivitamin use, postmenopausal hormone use, oral contraceptives use. 2. CVD mortality Not reported	

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures.**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders).**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls.**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders.**

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Ogdie, 2015	Unlikely	Unclear, not reported	Likely. Text comments reporting patient's death as CVD were classified as CV death. This was not validated.	Unlikely. Most important confounders were considered.

Li, 2012	Likely, population consists of registered nurses	Unclear, not reported	Unclear, not reported	Unlikely. Most important confounders were considered.

1. **Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.**
2. **2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The Risk of Bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.**
3. **Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.**

Noot 11: COPD

Evidencetabellen

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Outcome measures and effect size	Comments
Chen, 2015	Type of study: systemic review and meta-analysis Aim of the study is to quantify the magnitude of the association between overall and specific types of cardiovascular disease, major cardiovascular risk and COPD. Setting: 27 population based cohorts in America and Europe Source of funding: Non-commercial (Canadian Institutes of Health Research) Literature search until April 30, 2015	Inclusion criteria: Statistics available (prevalence of CVD and/or cardiovascular risk factors in COPD population plus or minus prevalence in matched control population) Stratified Study published in English Study located in a developed nation Study type indicated: prospective/retrospective, cohort, case-control, cross-sectional, longitudinal, ect. Data source indicated: administrative, clinical, etc. QAT points were assigned for quality and transparency of data and collection methods Enrollment period indicated: year(s) of study commencement and termination: Setting centres indicated: number of sites for subject recruitment Inclusion criteria listed	COPD	Inclusion period 1 – 26 years The review is unclear about incomplete data.	All outcomes are in OR (95%-CI) <u>Cardiovascular events</u> N = (COPD/controls) 122.646/449.027 2,46 (2,02 to 3,00) <u>ischaemic heart disease</u> 2,28 (1,76 to 2,96) <u>coronary heart disease</u> 1,86 (1,51 to 2,30) <u>myocardial infarction</u>	Amstar 8 uit 11

		QAT points assigned for quality of inclusion criteria in N (COPD/Controls) = 255.882/2.326.240 N = 60.211 individual records Mean age: 59 yr Sex: 51% M / 49% F 46,788 Whites (78%) 7,200 Blacks (12%) 3,816 Asians (6%) 2,407 Hispanics (4%)			2,71 (1,69 to 4,35) <u>angina pectoris</u> 8,16 (3,08 to 21,59) <u>cardiac dysrhythmia</u> 1,94 (1,55 to 2,43) p <u>cerebrovascular disease</u> 1,32 (0,99 to 1,76) <u>heart failure</u> 2,57 (1,90 to 3,47) <u>diseases of pulmonary circulation</u> 5,14 (4,07 to 6,50)	

3. **16 van de 27 onderzoeken in de meta-analyse zijn van lage kwaliteit (QUADAS-score < 11).**
4. **De heterogeniteit is 84%, dit wijst op inconsistentie. In de Jack-Knife-analyse (uitsluiten van steeds een ander onderzoek) blijven de OR en de betrouwbaarheidsinterval boven de 1,5. Dit wijst erop dat de associatie sterk is. Daardoor is dan ook niet afgewaardeerd voor inconsistentie.**

Kwaliteit van meta-analyse

Onderzoek	Risico op bias	Inconsistentie	Indirectheid	Onprecies	Publicatie bias	Oordeel
Chen, 2015	Hoog[1]	Nee[2]	Nee	Nee	Nee	Matige kwaliteit

Noot 12: Jicht

Evidencetabellen

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Clarson, 2015b (individual study characteristics deduced from Clarson, 2015) PS. Study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of cohort studies *Literature search up to November 2012* **A**: Choi, 2007 **B**: Krishnan, 2008 **C**: Kuo, 2010 **D**: Teng, 2012 <u>Study design</u>: Not reported <u>Setting and Country</u>: Not reported <u>Source of funding:</u> Non-commercial (this review); not reported per included study	Inclusion criteria SR: • Trial or epidemiological design (cohort, cross-sectional) • Included adults aged 18 and over • Examined the association of interest in a cohort of patients free from vascular disease at diagnosis of gout. Exclusion criteria SR: • Case-control studies due to the likelihood of sampling and recall bias associated with this design *Six studies included of which four studies reported outcomes on mortality due to CVD* <u>Important patient characteristics at baseline</u>:	Gout definition: **A**: Self report of physician diagnosis **B**: Self report or physician diagnosis + documented Sustained hyperuricaemia OR use of gout medication in the preceding 5y OR self report of gout without urate level **C**: Physican recorded (either crystals present in joint aspirate or ICD-9 gout code) OR self-report **D**: Self-report of physician diagnosis + self-report of elevated serum urate self-report of dietary advice for gout	Without gout	<u>End-point of follow-up</u>: **A**: 12 years **B**: 17 years **C**: 4,7 years **D**: 8,1 years <u>For how many participants were no complete outcome data available?</u> Not reported	<u>Outcome measure-1</u> Defined as mortality due to CVD Definitions per study (N deaths) (ICD-9 codes 390 to 459; ICD-10 codes I00 to I99): A: All cardiovascular deaths (2132) B: Death from any cardiovascular end-point (1241) C: Cardiovascular mortality (198) D: All cardiovascular deaths (1526) Effect measure, adjusted for vascular risk factors: HR (95%-CI): **A**: 1,38 (1,15 to 1,66) **B**: 1,21 (0,99 to 1,49) **C:** 1,97 (1,08 to 3,59) **D:** 1,23 (0,97 to 1,56) Pooled effect (random effects model): 1,29 (95%-CI 1,13 to 1,44)	<u>Facultative</u>: Author's conclusion: "Whilst observational studies cannot demonstrate causation, this meta-analysis of large, high-quality cohort studies strongly supports gout as an independent risk factor for mortality from CVD. The clinical implications of this review are the need to promote identification and management of cardiovascular risk factors in patients with gout, but also to identify and optimally manage gout in patients at risk of CVD." Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question:

		N, mean age (SD) **A**: 47.258 patients; I: 59, C: 54 yrs **B**: 9105 patients; I: 52,9 (5,8), C: 52,1 (5,9) yrs **C**: 49.332 patients; I: 52 (11), C: 50 (11) yrs **D:** 47.035 patients; I: 61,5 (7,7), C: 61,6 (8,0) yrs *Sex:* **A**: 100% Male **B**: 100% Male **C**: 53% Male **D:** 41% Male				Heterogeneity (I^2): 0,0% (p = 0,541) Outcome measure-2 Defined as morbidity due to CVD Not reported	• Risk of Bias was assessed with the Newcastle-Ottawa scale (bias due to unclear definition of exposure was not considered) • Three of the four studies appropriately adjusted for the predefined confounding variables, although all failed to adjust for kidney function. Level of evidence: as this review could be updated with one study, the level of evidence was graded with addition of this RCT.

Study **First author, year**	**Appropriate and clearly focused question?[1]** **Yes/no/unclear**	**Comprehensive and systematic literature search?[2]** **Yes/no/unclear**	**Description of included and excluded studies?[3]** **Yes/no/unclear**	**Description of relevant characteristics of included studies?[4]** **Yes/no/unclear**	**Appropriate adjustment for potential confounders in observational studies?[5]** **Yes/no/unclear/notapplicable**	**Assessment of scientific quality of included studies?[6]** **Yes/no/unclear**	**Enough similarities between studies to make combining them reasonable?[7]** **Yes/no/unclear**	**Potential risk of publication bias taken into account?[8]** **Yes/no/unclear**	**Potential conflicts of interest reported?[9]** **Yes/no/unclear**
Clarson, 2015b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No, only for the review

1. Research question (PICO) and inclusion criteria should be appropriate and predefined.

2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched.**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons.**
4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported.**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs).**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, Risk of Bias table et cetera).**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (for example Chi-square, I2)?.**
8. **An assessment of publication bias should include a combination of graphical aids (for example funnel plot, other available tests) and/or statistical tests (for example Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Study reference	**Study characteristics**	**Patient characteristics[2]**	**Intervention (I)**	**Comparison / control (C)[3]**	**Follow-up**	**Outcome measures and effect size[4]**	**Comments**
CVD mortality							
Kok, 2012	Type of study: cohort study Setting: Taiwan National Health Insurance Research Database Country: Taiwan Source of funding: Non-commercial	<u>Inclusion criteria</u>: • Aged 50 and above • Sought medical services from the Taiwan National Health Insurance system <u>Exclusion criteria</u>: • Subjects with incomplete data or null value • Subjects suffering from a severe form of CVD or diseases during the preceding year • Subjects with either type 1 or type 2 diabetes	Gout-related diagnoses The following codes under ICD-9-CM were included: • 274.0 gouty arthropathy • 274.1 gouty nephropathy • 274.89 gouty iritis • 274.8 gouty tophi • 274.11 uric acid nephrolithiasis Validation of these physician-diagnosed gout was ensured by verification that there were at least three separate outpatient visits by the same individual.	Without a gout-related diagnosis Same validation process as with gout-related diagnoses	<u>Length of follow-up</u>: ➢ 90% follow-up for 4 years <u>Incomplete outcome data</u>: Complete data was a selection criteria. 5,6% of enrolees had not complete data.	<u>Outcome measure-1</u> Defined as mortality due to CVD Number of CVD deaths (%) I: 5650 (3) C: 74.367 (2) Adjusted HR: 1,10 (1,07 to 1,13) <u>Outcome measure-2</u> Defined as morbidity due to CVD	The National Death Registry was used to confirm survival of included participants. Covariates in Cox regression models: gender, age, smoking-related diagnosis as a surrogate for cigarette smoking history and alcoholism-related diagnoses as a surrogate for chronic alcoholism history, hypertension, hyperlipidemia, atrial fibrillation and Charlson's co-morbidity index (CCI) score.

		N total at baseline: Intervention: 164,463 Control: 3,694,377 Important prognostic factors[2]: Age (I/C): 50 to 59: 33%/46% 60 to 69: 31%/28% 70 to 79: 27%/19% ≥ 80: 9%/7% Sex: I: 76% M C: 47% M Comorbidities (I/C) Hypertension: 28%/10% Hyperlipidemia: 6%/1%				Not reported	
CVD morbidity							
Janssens, 2017	Type of study: Cohort study Setting: Primary care patients Country: The Netherlands	Inclusion criteria: • ICPC code for gout (T92) • Free of prior CVD at baseline • Follow-up data available between 1st January 2008 till 28 February 2014	Gout (based on ICPC code T92)	Non-gout	Length of follow-up: Gout: Mean 29,8 months (SD 20,2) Non-gout: mean 26,8 months (SD 19,9)	Outcome measure-1 Defined as mortality due to CVD Not reported Outcome measure-2	Adjusted for age, sex and comorbidities (hypertension, diabetes mellitus, hypercholesterolemia).

	Source of funding: None received	N total at baseline: Intervention: 1859 Control: 6334 Important prognostic factors[2]: Age ± SD: I: 58 (14) C: 58 (14) Sex: I: 72% M C: 65% M Comorbidities (I/C) Hypertension: 39%/22% Diabetes mellitus: 15%/9% Hyperlipidemia: 10%/7%			Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Defined as morbidity due to CVD Number of CVD (%) I: 154 (8) C: 318 (3) Adjusted HR: 1,44 (1,18 to 1,76)	
Clarson, 2015a	Type of study: Cohort study Setting: Primary care patients Country: UK Source of funding: non-commercial	Inclusion criteria: • Aged over 50 at baseline • Incident diagnosis of gout • Consulting primary care between 1987 and 1999 Exclusion criteria: • Previous history of vascular disease	Gout (based on diagnostic code for gout in CPRD)	Non-gout	Length of follow-up: Not reported Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Outcome measure-1 Defined as mortality due to CVD Not reported Outcome measure-2 Defined as morbidity due to CVD	

		N total at baseline: Intervention: 8386 Control: 39766 Important prognostic factors[2]: Age ± SD: I: 66 (11) C: 66 (11) Sex: I: 69% M C: 69% M Comorbidities (I/C) Hypertension: 36%/17% Hyperlipidemia: 6%/3% Diabetes: 4%/4%				Number of CVD (%) Not reported Men: Adjusted HR: 0,95 (0,83 to 1,09) Women: Adjusted HR: 1,17 (0,99 to 1,38)	

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures.**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders).**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls.**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders.**

Study reference (first author, year of publication)	Bias due to a non-representative or ill-defined sample of patients?[1] (unlikely/likely/unclear)	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?[2] (unlikely/likely/unclear)	Bias due to ill-defined or inadequately measured outcome ?[3] (unlikely/likely/unclear)	Bias due to inadequate adjustment for all important prognostic factors?[4] (unlikely/likely/unclear)
CVD mortality				
Kok, 2012	Unlikely	Unlikely	Unlikely	Likely; risk factor-related diagnosis was used instead of adjustment for the risk factor
CVD morbidity				
Janssens, 2017	Unlikely	Unclear	Unlikely	Likely, analyses not adjusted for smoking or alcohol use or kidney function
Clarson, 2015a	Unlikely	Unclear	Unlikely	Unlikely

1. **Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.**
2. **2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The Risk of Bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.**
3. **Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.**

Noot 13: Reumatoïde artritis

Evidencetabellen

A. Evidence table for systematic review of RCTs and observational studies (prognosis studies)

Study reference	Study characteristics	Patient characteristics	Prognostic factor	Follow-up	Outcome measures and effect size	Comments
Cardiovasculaire morbiditeit en mortaliteit						
Avina-Zubieta, 2012	SR van observationeel onderzoek	Inclusiecriteria SR: - observationeel onderzoek - vooraf gedefinieerde RA criteria	Reumatoïde artritis	Follow-up (jaren): Bij 9 onderzoeken was de gemiddelde follow-up 4,7 jaar (range 1 to 15 jaren)	**Cardiovasculaire morbiditeit en mortaliteit***: pooled RR 1,48 (95%-BI 1,36 to 1,62)	Conclusies auteurs: "In summary, our meta-analysis of published observational

	Literatuur search vanaf startdatum databases (Medline, Embase, LILACS, Cochrane) tot juni 2011 Setting, country: USA, UK, Zweden, Canada en Nederland Type of funding: Not reported	- vooraf gedefinieerde HVZ criteria voor een eerste event van MI, CVA of hartfalen - RR berekeningen - vergelijkende groep - patiënten zonder HVZ Exclusiecriteria SR: - geen Belangrijkste baseline karakteristieken van individuele onderzoeken: 16 onderzoeken, waarvan 9 onderzoeken het risico op cardiovasculaire morbiditeit onderzochten N, leeftijd (range gemiddeld in jaren): 41.490, 46,3 to 64,1 *Geslacht:* 62 tot 100% vrouw	Definitie diagnose RA: op basis van American College of Rheumatology (ACR) classificatie criteria of andere gevalideerde score	Bij de overige 5 onderzoeken was de follow-up niet bekend Incomplete data Niet gerapporteerd Event rate: 5,1%	* definitie: Fataal en niet-fataal • myocardinfarct • CVA • hartfalen Heterogeniteit (Q) 25,6 (p = 0,0009)	studies indicates that people with RA have a 48% (pooled RR 1,48 (95%-CI 1,36 to 1,62)) increased risk of incident CVD when compared to the general population." Persoonlijke opmerkingen over studiekwaliteit, conclusies en andere problemen (mogelijk) die relevant zijn voor de onderzoeksvraag: Er was een significante hetereogeniteit van de onderzoeken, dat deels werd toegeschreven aan het verschil in soort cohort (de RR was lager in de inception cohorten) en niet aan het verschil in kwaliteit. De gemiddelde follow-up was relatief kort. De kwaliteit van de SR was goed (AMSTAR 10/11). Niveau van bewijs: GRADE (per vergelijking en uitkomst maat, inclusief redenen voor af/opwaarderen)

						<u>Uitkomst cardiovasculaire morbiditeit:</u> Deze uitkomst wordt geüpdatet met de 3 geselecteerde cohorten. <u>Uitkomst cardiovasculaire mortaliteit:</u> Deze uitkomst wordt geüpdatet met 1 geselecteerd cohort.

ACR = American College of Rheumatology, ARA = American Rheumatism Association, SMR = gestandaardiseerde mortaliteitsratio

B. Evidencetabel voor prognostische onderzoeken (observationeel)

Research question:

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Outcome measures and effect size	Comments
Cardiovasculaire morbiditeit						
Lindhardsen, 2011	Type of study: nationwide cohort, nested case-controle onderzoek Setting en country: population of Denmark Source of funding: unrestricted grant from the Danish Rheumatism Association	<u>Interventiegroep:</u> Patiënten met reumatoide artritis <u>Vergelijkende groep:</u> Patiënten zonder reumatoide artritis <u>Interventiegroep:</u> N = 9921 Sex: 71 % (F) Gemiddelde leeftijd: 56 jaar <u>Vergelijkende groep:</u>	Rheumatoide arthritis Definitie diagnose RA: identified by ICD codes M5-M6 in combination with a dispensed prescription of disease-modifying antirheumatic drugs (DMARDs), that is, methotrexate (ATC classes L01BA01 and L04AX03), sulfasalazine	Gemiddelde follow-up (SD): 4,6 (2,8) Incomplete data: 0,04%	**Cardiovasculaire morbiditeit <u>myocardinfarct</u>:** incidence rate ratio: 1,7 (95%-BI 1,5 to 1,9)*	* Gecorrigeerd voor geslacht, leeftijd, calendar year, cardioprotective medication, comorbiditeit and socioeconomische status.

		N = 3.978.821 Sex: 51% (F) Gemiddelde leeftijd: 46 jaar	(A07EC01), azathioprine (L04AX01), hydroxychloroquine (P01BA02), gold therapy (M01CB), lefl unomide (L04AA13) and cyclosporine (L04AA01), within a year before or after the time of diagnosis[1]			
Castaneda, 2015	Type of study: prospective cohort study Setting: Cardiovascular in rheumatology (CARMA) project Country: Spain Source of funding: Commercial (Abbvie) and non-commercial	<u>Interventiegroep:</u> Patients with a diagnosis of rheumatoid arthritis (RA), ankylosing spondylitis or psoriatic arthritis without a history of CVD <u>Vergelijkende groep</u>: Individuals without these disorders but with osteoarthritis, osteoporosis or other non-inflammatory diseases matched by age and sex <u>Interventiegroep</u> N = 775 deelnemers Sex: 75% F Mean age ± SD: 57 ± 12 <u>Vergelijkende groep</u> N = 677 deelnemers Sex: 65% F Mean age ± SD: 54 ± 12	Rheumatoide arthritis Definitie diagnose RA: inclusie obv de American College of Rheumatology Classification Criteria for RA	Einde van follow-up: 10 jaar <u>Incomplete data</u>: geen	**Cardiovasculaire morbiditeit#** OR: 1,58 (95%-BI 0,90 to 2,76)* <u>#definitie cardiovasculaire morbiditeit</u>: • ischemische hartziekten • beroerte • perifeer arterieel vaatlijden • hartfalen	* De berekende odds ratio's werden gecorrigeerd voor geslacht, leeftijd ten tijde van inclusie, leeftijd bij het begin van symptomen, niveau van scholing, rookstatus, familiaire belasting met ischemische hartziekten, duur van de ziekte, botaantasting, Health Assessment Questionnaire en obesitas, hypertensie, diabetes en dyslipidemie.

Ogdie, 2015	Type of study: prospective cohort study Setting: The Health Improvement Network (THIN), a primary care medical record database Country: UK Source of funding: Non-commercial	<u>Interventiegroep:</u> Patients with a diagnosis of rheumatoid arthritis (RA), ankylosing spondylitis or psoriatic arthritis between 18 and 89 years of age <u>Vergelijkende groep:</u> Individuals without these disorders matched on practice and index date within the practice. <u>Interventie groep:</u> *No DMARDS:* N = 17912 participants Sex: 30% M Mean age ± SD: 64 ± 16 *DMARDS:* N = 23840 participants Sex: 30% M Mean age ± SD: 60 ± 14 <u>Vergelijkende groep</u> N = 81.573 participants Sex: 45% M Mean age ± SD: 50 ± 18	Rheumatoid arthritis Definition diagnosis RA: diagnosis defined by the READ code, i.e. standard medical diagnosis codes used in the UK practice.	Duur follow-up (mean (SD)): Interventiegroep No DMARDS: 5,40 (3,99) DMARDS:5,36 (3,80) Controlegroep 5,24 (3,92) <u>Incomplete data</u>: niet vermeld	**Cardiovasculaire morbiditeit** <u>Myocardinfarct</u> No DMARDS HR 1,33 (95%-CI 1,17 to 1,52)* DMARDS HR 1,96 (95%-CI 1,75 to 2,19)* <u>CVA</u> No DMARDS HR 1,29 (95%-CI 1,15 to 1,45)* DMARDS HR 1,24 (95%-CI 1,10 to 1,39)*	* Adjusted for sex, age, hypertension, hyperlipidemia, diabetes and start year in the cohort.
Cardiovasculaire mortaliteit						
Ogdie, 2015	Zie boven	Zie boven	Zie boven	Zie boven	**Cardiovasculaire mortaliteit**	* Adjusted for sex, age, hypertension, hyperlipidemia, diabetes and start year in the cohort.

					No DMARDS HR 1,43 (95%-CI 1,28 to 1,59)* DMARDS HR 1,66 (95%-CI 1,48 to 1,86)*	

[1] Deze methode is gevalideerd in onderzoek met een positief voorspellende waarde van > 80% (Singh, 2004).

C. Table of quality assessment – prognostic studies

(The criteria used in this checklist are adapted from: Altman DG (2001). Systematic reviews of evaluations of prognostic variables. In: Egger M, Smith GD, Altman DG (eds.). Systematic reviews in health care. London: BMJ Books; Laupacis A, Wells G, Richardson WS, Tugwell P (1994). Users' guides to the medical literature. How to use an article about prognosis. Evidence-Based Medicine Working Group. JAMA,272:234-7)

Research question: Reumatoide artritis

Study reference (first author, year of publication)	**Was there a representative and well-defined sample of patients at a similar point in the course of the disease?** (yes/no/unclear)	**Was follow-up sufficiently long and complete?** (yes/no/unclear)	**Was the outcome of interest defined and adequately measured?** (yes/no/unclear)	**Was the prognostic factor of interest defined and adequately measured?** (yes/no/unclear)	**Was loss to follow-up / incomplete outcome data described and acceptable?** (yes/no/unclear)	**Was there statistical adjustment for all important prognostic factors?** (yes/no/unclear)	**Level of evidence**
Lindhardsen, 2011	Yes	Yes	Yes	Yes	Yes	Yes	A2
Castaneda, 2015	Yes	Yes	Yes	Yes	Yes	Yes	B
Ogdie, 2015	Yes	No	Yes	Yes	No (not described)	Yes	B

A1: Meta-analysis of at least 2 independent studies of level A2

A2: Prospective inception cohort* (patients enrolled at same point in disease course), adequate study size and follow-up (≥ 80%), adequate control for confounding and no selective loss to follow-up

B: Prospective cohort* but not fulfilling all criteria for category-A2, retrospective cohort study or, case-control study, or cross-sectional study

C: non-comparative study

*** untreated controls from a RCT can also be considered as a cohort**

Noot 14: Ziekte van Bechterew

Evidencetabellen

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Outcome measures and effect size	Comments
Dregan, 2017	Type of study: prospective cohort study Setting: UK Biobank data Country: UK Source of funding: Non-commercial (National Institute for Health Research Biomedical Research Center)	<u>Exposed group:</u> Participants of UK Biobank reporting a previous diagnosis of RA, SLE, psoriasis, AS, systemic vasculitis, Crohn's disease and UC disorders Comparison: those reporting none of these disorders <u>Exposed group</u> N = 19.082 participants Ankylosing spondylitis, N = 1400 (7%) Sex: 62% M Mean age ± SD: 37 ± 13 <u>Unexposed group</u> N = 483.559 participants Sex: 46% M Mean age ± SD: 57 ± 8	Ankylosing spondylitis (also Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis)	Endpoint of follow-up: not reported For how many participants were no complete outcome data available? < 0,01%	<u>Cardiovascular disease related mortality</u> Ankylosing spondylitis Adjusted RR (95%-CI)*: 1,97 (1,33 to 2,90) <u>All cause mortality</u> Ankylosing spondylitis Adjusted HR (95%-CI)*: 1,31 (1,00 to 1,71)	* Adjusted for age, sex, deprivation, ethnicity and educational level.
Hung, 2016	Type of study: prospective cohort study Setting: Taiwan National Health Insurance Research Database	<u>Exposed group:</u> Principal diagnosis between January 2001 and December 2005 of ankylosing spondylitis in ambulatory care and inpatients care, with ≥ 1 inpatient admission or 2 ambulatory visits.	Ankylosing spondylitis (ICD-9-CM code 720 or 720.0)	Endpoint of follow-up: maximum 5 year (2000 to 2005)	<u>Cardiovascular disease (5 yr)</u> Ankylosing spondylitis Crude HR (95%-CI): 1,24 (1,05 to 1,46)	* Adjusted for sex, age, urbanization level, geographic region, hypertension, hyperlipidemia, and diabetes.

	Country: Taiwan Source of funding: Non-commercial	Only patients ≥ 40 yr. Comparison: matches with the AS cohort on age and gender. <u>AS group</u> N = 537 participants Sex: 48% M Age 40-49 = 49% <u>Non-AS group</u> N = 2685 participants Sex: 48% M Age 40 to 49 = 49%			Adjusted HR (95%-CI)*: 1,20 (1,02 to 1,42)	AS = ankylosing spondylitis
Haroon, 2015	Type of study: retrospective cohort study Setting: 4 core datasets from Ontario's provincial health administrative database Country: Canada Source of funding: Non-commercial	<u>Exposed group:</u> ≥ 2 OHIP claims, ICD-9-CM code 720 over 2 years, or ICD-10 code M45. Only patients > 15 yr. Between April 1995 and March 2011 Comparison: match on age and sex assigned same cohort entry date, 4 comparators for each AS patient. <u>AS group</u> N = 21.473 participants Mean age ±SD: 45,6 yr±15,9 <u>Non-AS group</u> N = 86.606 participants Mean age ±SD: 45,7 yr±16,0	Ankylosing spondylitis (ICD-9-CM code 720.0 or ICD-10 code M45)	<u>Mean length of follow-up:</u> AS group: 166.920 patient-years Non-AS group: 1686.461 patient years For how many participants were no complete outcome data available? Not reported	<u>Cardiovascular mortality</u> Crude HR (95%-CI): 1,35 (1,07 to 1,70) <u>Vascular mortality</u> Crude HR (95%-CI): 1,43 (1,19 to 1,72) Adjusted HR (95%-CI)*: 1,36 (1,13 to 1,65)	* Adjusted for baseline CKD, PVD, hypertension, IBD, diabetes, dementia, cancer
Szabo, 2011	Type of study: retrospective cohort study	<u>Exposed group:</u>	Ankylosing spondylitis (ICD-9-CM code 720.0)	<u>Mean length of follow-up:</u>	<u>Cerebrovascular disease (10 yr)</u>	* Adjusted for sex and age

	Setting: Régie de l'Assurance Maladie du Québec (RAMQ) database and the Quebec provincial hospital discharge (MED-ÉCHO) database Country: Canada Source of funding: Non-commercial	≥ 1 diagnosis of AS ICD-9 code 720.0 between January 1996 and December 2006. Only patients > 19 yr. Comparison: 1% random sample of RAMQ cohort (without AS). <u>AS group</u> N = 8616 participants Mean age: 42,5 yr <u>Non-AS group</u> N = 50.699 participants Mean age: 42,5 yr		AS group: 10,2 yr Non-AS group: 10,5 yr For how many participants were no complete outcome data available? Not reported	Standardized Prevalence Ratio, SPR (95%-CI)*: 1,25 (1,15 to 1,35) <u>Other cardiovascular disease (10 yr)</u> SPR (95%-CI)*: 1,36 (1,29 to 1,44) <u>Congestive heart disease (10 yr)</u> SPR (95%-CI)*: 1,34 (1,26 to 1,42) <u>Ischemic heart disease (10 yr)</u> SPR (95%-CI)*: 1,37 (1,31 to 1,44) <u>Aortic valvular heart disease (10 yr)</u> SPR (95%-CI)*: 1,58 (1,31 to 1,91) <u>Non-aortic valvular heart disease (10 yr)</u> SPR (95%-CI)*: 1,58 (1,43 to 1,74)	AS = ankylosing spondylitis SPR = Standardized Prevalence Ratio

Table of quality assessment – prognostic studies

(The criteria used in this checklist are adapted from: Altman DG (2001). Systematic reviews of evaluations of prognostic variables. In: Egger M, Smith GD, Altman DG (eds.). Systematic reviews in health care. London: BMJ Books; Laupacis A, Wells G, Richardson WS, Tugwell P (1994). Users' guides to the medical literature. How to use an article about prognosis. Evidence-Based Medicine Working Group. JAMA,272:234-7)

Study reference (first author, year of publication)	**Was there a representative and well-defined sample of patients at a similar point in the course of the disease?** (yes/no/unclear)	**Was follow-up sufficiently long and complete?** (yes/no/unclear)	**Was the outcome of interest defined and adequately measured?** (yes/no/unclear)	**Was the prognostic factor of interest defined and adequately measured?** (yes/no/unclear)	**Was loss to follow-up / incomplete outcome data described and acceptable?** (yes/no/unclear)	**Was there statistical adjustment for all important prognostic factors?** (yes/no/unclear)	**Level of evidence**
Dregan, 2017	Yes	Unclear	Yes	No (self-reported)	Yes	Yes	A2
Hung, 2016	Yes	No	Yes	Yes	No (not described)	Yes	B
Haroon, 2015	Yes	Yes	Yes	Yes	No (not described)	No	B
Szabo, 2011	Yes	Yes	Yes	Yes	No (not described)	No	B

Noot 15: Hiv

Evidencetabellen

Study reference	**Study characteristics**	**Patient characteristics**	**Prognostic factor(s)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Islam, 2012	Meta-analyse 20 onderzoeken Relevante eindpunten: A. Risico op HVZ bij hiv-geïnfecteerden versus niet-geïnfecteerden (3 onderzoeken) B. Risico op HVZ bij hiv-geïnfecteerden behandeld met retrovirale medicatie versus niet-geïnfecteerden (3 onderzoeken) C. Risico op HVZ bij hiv-geïnfecteerden behandeld met retrovirale medicatie versus hiv-geïnfecteerden (8 onderzoeken)	Inclusiecriteria: - Cohortonderzoeken of randomized clinical trials - Hiv-geïnfecteerde volwassenen in een onderzoeksarm - Eindpunt hartziekte - Antiretrovirale medicatie - Uitkomsten in RR, OR of HR Exclusiecriteria: - Geen uitkomsten in RR, OR of HR - Niet-Engels	HIV-infectie	Eindpunt A: 4-5,8 jaar Eindpunt B: 6,5-11 jaar	Eindpunt A Events HIV/control 1. ?/? 2. 48/11 3. 189/26.142 Effect size RR 1,61 (95%-BI 1,43-1,81) Eindpunt B Events	Kwaliteit van bewijs: Amstar 8 uit 11 Eindpunt A: lage kwaliteit Eindpunt B: lage kwaliteit Eindpunt C: matige kwaliteit

		Eindpunt A 3 Onderzoeken 1. Cohort 2. Cohort 3. Cohort HIV/control 1. 3953/373.856 2. 3851/1.044.589 3. 74.958/? Leeftijd 1. 49,5 jaar 2. 38,9 jaar 3. 38 jaar Ziekte 1. Myocardinfarct 2. Ischemische hartziekte 3. Myocardinfarct Eindpunt B 3 onderzoeken 1. Cross-sectionaal 2. Cohort 3. Cohort HIV/Control 1. 80/256 2. 6702/72.480 3. 1191/1751 Leeftijd 1. 34 jaar 2. 39,4 jaar 3. 39,1 jaar Ziekte 1. HVZ 2. Myocardinfarct 3. Myocardinfarct Eindpunt C 1. Cross-sectional			HIV/Control 1. 33/43 2. ?/? 3. 36/31 Effect size RR 2,00 (95%-BI: 1,70-2,37) Eindpunt C Events HIV/Control 1. ?/? 2. ?/? 3. ?/? 4. ?/? 5. 289/884 6. ?/? 7. 36/31 8. ?/? Effect size RR 1,52 (95%-BI: 1,35-1,70)	

		2. Cohort 3. Cohort 4. Case-control 5. Case-control 6. Cohort 7. Cohort 8. Cohort HIV/control 1. 1021/? 2. 41213/? 3. 28513/? 4. 6168/? 5. 74958/? 6. 34976/? 7. 1191/1751 8. 33308/? Leeftijd 1. 41 jaar 2. 45 jaar 3. 26 jaar 4. 52.1 jaar 5. 47 jaar 6. 37,7 jaar 7. 39,1 jaar 8. 49 jaar Ziekte 1. HVZ 2. HVZ 3. Coronaire hartziekte 4. Myocardinfarct 5. Myocardinfarct 6. Myocardinfarct 7. Myocardinfarct 8. Myocardinfarct				

Eindpunt het risico op HVZ bij hiv-geïnfecteerden versus niet-hiv-geïnfecteerden

Onderzoek	Risico op bias	Inconsistentie	Indirectheid	Imprecisie	Publicatiebias	Oordeel
Islam, 2012	hoog[1]	Nee	Nee	Nee	Laag risico	Lage kwaliteit

Eindpunt het risico op HVZ bij hiv-geïnfecteerden behandeld met antiretrovirale medicatie versus niet-hiv-geïnfecteerden

Onderzoek	Risico op bias	Inconsistentie	Indirectheid	Imprecisie	Publicatiebias	Oordeel
Islam, 2012	Zeer hoog[1]	Nee	Nee	Nee	Laag risico	Lage kwaliteit

Eindpunt Risico op HVZ bij hiv-geïnfecteerden behandeld met retrovirale medicatie versus hiv-geïnfecteerden zonder retrovirale medicatie

Onderzoek	Risico op bias	Inconsistentie	Indirectheid	Imprecisie	Publicatiebias	Oordeel
Islam, 2012	Laag	Nee	Nee	Nee	Laag risico	Matige kwaliteit

5. **Er zijn 3 onderzoeken gebruikt in de meta-analyse voor dit eindpunt. De kwaliteit van 1 in onderzoek is laag (Obel, 2007). De hiv-groep is vergeleken met de algemene populatie en zijn niet gematcht met een vergelijkbare groep. Het onderzoek corrigeert voor meerdere confouders, maar niet voor roken (Obel, 2007).**
6. **De gebruikte onderzoeken (N = 3) in de meta-analyse met als vergelijking het risico op HVZ bij hiv-geïnfecteerden versus niet-hiv-geïnfecteerden zijn van lage kwaliteit. De hiv-groep is vergeleken met de algemene populatie en zijn niet gematcht met een vergelijkbare groep in 2 onderzoeken (Lang, 2010; Obel 2007). In 1 onderzoek is er geen correctie voor confounders gedaan, behalve leeftijd en geslacht.**

Noot 16: IBD

Evidencetabellen

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Singh, 2014 PS Individuele studiekarakteristieken en resultaten zijn geëxtraheerd uit de	SR van cohort studies en case-control studies *Literatuur search tot 1 maart 2013* A: Andersohn, 2010	Inclusiecriteria SR: - Goed gedocumenteerde diagnose CD of CU - Gerapporteerde incidente CVA's, isch hartziekte (IHD) of perifeer arterieel vaat event (niet intestinaal) - Controlegroep of referentiegroep non-IBD aanwezig	Interventie Diagnose IBD	Controle Geen diagnose IBD	<u>Tijdsperiode/Follow-up (jaren)</u>: A 5,2 – 5,4 jr B 16,1 – 16,6 jr C 3,2 – 4,1 jr D 6,0 – 6,2 jr E 4,4 – 4,7 jr F 12 jr (cohort) G 4,3 – 4,5 jr H 21 jr (cohort)	<u>Uitkomstmaten</u> A: CVA B: CVA/IHD/PAD C: CVA/IHD/PAD D: CVA E: IHD F: IHD G: IHD H: CVA/IHD <u>Effectmaten</u>	Author's conclusion: 'IBD is associated with a modest increase in the risk of cardiovascular morbidity (from CVA and IHD), particularly in women. These patients should be counselled routinely on aggressive risk factor modification.'

SR, tenzij anders aangegeven	B: Bernstein, 2008 C: Ha, 2009 D: Kristensen, 2013 E: Osterman, 2011 F: Rungoe, 2012 G:Yarur, 2011 H: Zoller, 2012 <u>Study design</u>: SR A nested case-control (C-C) B nested C-C C nested C-C D nested C-C E nested C-C F cohort G case-control H cohort <u>Setting and Country</u>: USA (SR) A: UK, population B: Canada, population	- Effectmaten: RR, OR of gestandaardiseerde incidence rate, met 95%-CI Exclusiecriteria SR: - Crosssectionele studies - Geen 95%-CI - Indien meerdere publicaties zelfde cohort: alleen meest recente <u>Belangrijkste baseline karakteristieken van individuele studies</u>: <u>N (IBD/controles)</u> A 8054/161.078 B 8072/80.489 C 17.487/69.948 D 20.795/199.978 E 25.327/237.592 F 28.833/4.541.987 G 356/712 H 43.832/43.832			<u>Aantal events (cases/controles):</u> A • CVA 89/1670 B • CVA 161/1390 • IHD 238/1884 • PAD 33/ 255 C • CVA 496/1804 • IHD 168/4219 • PAD 115/397 D • CVA 456/3327 E • IHD 390/3096 F • IHD 863/243.844 G • IHD 47/33 H • CVA 1222/pop.est. • IHD 3872/pop.est.	- ORs adjusted (95%-CI) CVA: 1,18 (1,09-1,27) IHD: 1,18 (1,07-1,31) PAD: 1,15 (0,96-1,38)	Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question: - matig tot sterke heterogeniteit (I^2 53% CVA en 88% IHD (met outlier)); AMSTAR 10/11 Level of evidence: GRADE (per comparison and outcome measure) including reasons for down/upgrading. Uitkomsten: Downgrade met 1 niveau vanwege grote heterogeniteit?

	C: USA, health claims database D: Denemarken, population E: UK, population F: Denemarken, population G: USA, hospital based H: Zweden, population <u>Source of funding:</u> Niet commercieel (deze SR); niet gerapporteerd per studie						
Xiao, 2015 PS Individuele studiekarakteristieken en resultaten	SR van cohort studies en case-control studies *Literatuur search tot 1 mei 2015*	Inclusiecriteria SR: 1/ Gepubliceerde, peer reviewed data van cohort of case-control design 2/ Goed gedocumenteerde diagnose CU of CD	Interventie Diagnose IBD	Controle Geen diagnose IBD	<u>Tijdsperiode/Follow-up (jaren)</u>: A 1984-2003 B 1987-2005 C: 1987-2008 D: 2002-2013 E: 1995-2005 F: 1998-2011	<u>Uitkomstmaten</u> A tot en met H: CVA <u>Effectmaten</u> - gepoolde overall HR 1,29 (95%-BI 1,16 tot 1,43) I^2 0,84 = hoog	Author's conclusion: 'our meta-analysis demonstrated a modest increase in risk of stroke in patients with IBD, especially higher in females and in younger Asian patients, although our analysis showed a

zijn geëxtraheerd uit de SR, tenzij anders aangegeven	A: Bernstein, 2008 B: Andersohn, 2010 C: Zoller, 2012 D: Dregan, 2014 E: Keller, 2014 F: Huang, 2014 G: Kristensen, 2014 H: Keller, 2015 <u>Study design</u>: SR A en C tot en met H: cohort B: nested case-control <u>Setting and Country</u>: China (SR) A: Canada B: UK C: Zweden D: UK E: Taiwan F: Taiwan G: Denemarken H: Taiwan	3/ Uitkomst CVA na de diagnose IBD 4/ Gem lftd deelnemers > 18 jaar 5/ gerapporteerde effectmaten in OR/RR/HR met 95%-BI Exclusiecriteria SR: 1/ CVA voor de diagnose IBD 2/ Geen 95%-CI berekenbaar <u>Belangrijkste baseline karakteristieken van individuele studies</u>: <u>N (IBD)</u> A: 8060 B: 8054 C: 43.832 D: 19.832 E: 516 F: 18.392 G: 24.499 H: 3309			G: 1996-2011 H: 1995-2005 <u>Aantal events (cases/controles):</u> Niet gerapporteerd	- gepoolde HR CD 1,32 (95%-BI 1,13 tot 1,56) I^2 0,86 = hoog - gepoolde HR CU 1.18 (95%-BI 1,06 tot 1,31) I^2 0,62 = matig hoog	considerable heterogeneity, and in concordance with previous meta-analyses.' Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question: - matig tot sterke heterogeniteit - AMSTAR 7/11 Level of evidence: GRADE (per comparison and outcome measure) including reasons for down/upgrading. Uitkomsten: Downgrade met 1 niveau vanwege grote heterogeniteit?

	Source of funding: Niet commercieel (deze SR); niet gerapporteerd per studie						

Grade beoordeling kwaliteit systematische reviews

Onderzoek	Risico op bias	Inconsistentie	Indirectheid	Onprecies	Publicatiebias	Oordeel
Singh, 2015	Laag	Nee	Nee	Nee	Nee	Hoog
Xia, 2015	Laag	Ja[1]	Nee	Nee	Nee	Matig

1. Heterogeniteit = 84%

Beoordeling cohortonderzoeken met Newcastle - Ottawa Quality Assessment Scale Cohort Studies

Onderzoek	1. Representativeness of the exposed cohort	2. Selection of the non exposed cohort	3. Ascertainment of exposure	4. Demonstration that outcome of interest was not present at start of study	5. Comparability of cohorts on the basis of the design or analysis (max 2 punten)	6. Assessment of outcome	7. Was follow-up long enough for outcomes to occur	8. Adequacy of follow up of cohorts	Score
Jussila, 2014	*		*	*		*	*		5 uit 9

1. **Truly representative of the average IBD in the community**
2. **No description of the derivation of the non exposed cohort**
3. **Secure record (eg surgical records)**
4. **Yes**
5. **Nee (2x)**
6. **Record linkage**
7. **Yes (select an adequate follow up period for outcome of interest)**
8. **No statement**

Noot 25: Streefwaarden van LDL-cholesterol

Evidencetabellen

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Schmidt, 2017 (individual study characteristics deduced from Schmidt, 2017) PS. Study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of RCTs *Literature search up to May 2016* **D**: FOURIER **S**: SPIRE 1/2 <u>Study design</u>: All were RCTs <u>Setting</u>: For all: outpatient care <u>Source of funding:</u> All RCTs were funded by pharmaceutical companies.	Inclusion criteria SR: • Parallel-group and factorial RCTs with follow-up of at least 24 weeks • Included adults 18 years of age or older, with or without a prior history of CVD • Randomised to a PCSK9 inhibitor or to placebo, statin, ezetimib of combination of these. Exclusion criteria SR: • Cluster RCTs, cross-over trails and non-randomised studies *20 studies included, of which five studies were only published as conference abstracts. These studies were excluded. A further 13 were excluded as the primary endpoint was not cardiovascular disease.* <u>Important patient characteristics at baseline</u>: <u>N, mean age</u> **D**: 27.564 patients, 63 (SD	**D**: Evolocumab **S**: Bococizumab Background therapy: **D**: Statin therapy **S**: Statins and/or ezetimib	**D**: Placebo **S**: Placebo	<u>End-point of follow-up</u>: **D**: 157 weeks **S**: 143 weeks <u>For how many participants were no complete outcome data available?</u> (intervention/control) **D**: Unclear **S**: Unclear	<u>Outcome measure-1</u> Defined as LDL Results on LDL levels were deduced from the individual trial publications <u>Outcome measure-2</u> Defined as CVD Results on LDL levels were deduced from the individual trial publications <u>Outcome measure-3</u> Defined as mortality due to CVD Results on LDL levels were deduced from the individual trial publications <u>Outcome measure-4</u> Defined as adverse events Results on LDL levels were deduced from the individual trial publications	**S**: Many participants were lost to follow-up due to antidrug antibody response

		9) yrs **S**: 27.438 patients, 63 (SD 9) yrs <u>Sex</u>: **D**: 75% Male **S**: 70% Male <u>History of CVD:</u> **D**: 27.564 (100%) **S**: 23.198 (85%) <u>Participants with FH:</u> **D**: NA **S**: 1072 (4%)					
Nuβbaumer, 2016 (individual study characteristics deduced from Nuβbaumer, 2016) PS. Study characteristics and results are extracted from the SR (unless stated otherwise)	See the full article for all relevant information https://www-ncbi-nlm-nih-gov.eur.idm.oclc.org/pubmed/27412989						

Chan, 2011 (individual study characteristics deduced from Chan, 2011) PS. Study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of RCTs *Literature search up to April 2009* **A**: De Lemos, 2004 **B**: Cannon, 2004 **C**: Pedersen, 2005 **E**: LaRosa, 2005 <u>Study design</u>: RCT (parallel) <u>Setting and Country</u>: Not reported <u>Source of funding:</u> Not reported for included studies; unclear what kind of funding the review received.	Inclusion criteria SR: • At least one of the aims was to lower lipid levels • Lipid lowering was intensive and that the target LDL-C was in the vicinity of < 2,1 mmol/l • Minimum follow-up period of 12 months post-intervention • Study population considered to be at high risk of vascular events • Data of the individual components of composite secondary end-points were available *7 studies included of which 3 were excluded as the primary endpoint was not cardiovascular disease* <u>Important patient characteristics at baseline</u>: <u>N, mean age</u> **A**: 4497 patients, 61 yrs **B**: 4162, 58 yrs **C**: 8888, 62 yrs **E**: 10.001, 61 yrs <u>*Sex:*</u> Not reported	**A**: Simvastatin 40 mg, 1m/80 mg **B**: Atorvastatin 80 mg **C**: Atorvastatin 80 mg **E**: Atorvastatin 80 mg	**A**: placebo, 4 m/ simvastatin 20 mg **B**: Pravastatin 40 mg **C**: Simvastatin 20 mg **E**: Atorvastatin 10 mg	<u>End-point of follow-up</u>: **A**: 0,5 to 2 years, median 2,0 years **B**: 1,5 to 3 years, mean 2 years **C**: 4,0 to 5.9 years, median 4.8 years **E**: Median 4,9 years <u>For how many participants were no complete outcome data available?</u> (intervention/control) Not reported	<u>Outcome measure-1</u> Defined as LDL-concentration, percent change from baseline (%) (mean LDL level during treatment (mmol/l) **A**: I: -41,03 (1,71) C: -27,18 (2,10) **B**: I: -41,61 (1,60) C: -10,22 (2,46) **C:** I: -34,08 (2,07) C: -17,83 (2,58) **E**: I: -20,72 (1,99) C: 3,16 (2,61) <u>Outcome measure-2</u> Defined as major coronary events*, odds ratio (95%-CI) **A**: 0,88 (0,75 to 1,03) **B**: 0,86 (0,74 to 0,99) **C**: 0,77 (0,70 to 0,85) **E**: 0,79 (0,68 to 0,91) <u>Outcome measure-3</u> Defined as cardiovascular/coronary heart disease deaths, odds ratio (9%CI) **A**: 0,74 (0,55 to 0,99)	* Definition of major cardiovascular events was not only an event of CVD, but also deaths. Authors' conclusions: In those at high risk of cardiovascular events, intensive lipid lowering with statins to LDL-C level < 2,1 mmol/l significantly reduces risk of stroke, major coronary events and CVD or CHD deaths compared to LDL-C level ≥ 2,1 mmol/l. Remarks: • All included trials included patients with CVD.

		Criteria: **A**: Post acute coronary syndrome **B**: Post acute coronary syndrome **C**: Previous MI **E**: Clinically evident CHD, LDL < 3,4				**B**: 0,78 (0,45 to 1,35) **C**: 0,98 (0,80 to 1,22) **E**: 0,79 (0,61 to 1,03) <u>Outcome measure-4</u> Defined as treatment discontinuation due to side effects, odds ratios (95%-CI) **A**: 1,19 (0,75 to 1,88) **B**: 0,89 (0,78 to 1,01) **C**: 2,43 (2,04 to 2,91) **E**: 1,39 (1,18 to 1,64)	

Risk of Bias tabel

Study **First author, year**	**Appropriate and clearly focused question?[1]** **Yes/no/unclear**	**Comprehensive and systematic literature search?[2]** **Yes/no/unclear**	**Description of included and excluded studies?[3]** **Yes/no/unclear**	**Description of relevant characteristics of included studies?[4]** **Yes/no/unclear**	**Appropriate adjustment for potential confounders in observational studies?[5]** **Yes/no/unclear/ notapplicable**	**Assessment of scientific quality of included studies?[6]** **Yes/no/unclear**	**Enough similarities between studies to make combining them reasonable?[7]** **Yes/no/unclear**	**Potential risk of publication bias taken into account?[8]** **Yes/no/unclear**	**Potential conflicts of interest reported?[9]** **Yes/no/unclear**
Schmidt, 2017	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes
Nuβbaumer, 2016	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	No	Yes
Chan, 2011	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Unclear

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined.**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched.**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons.**

4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported.**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs).**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, Risk of Bias table et cetera).**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (for example Chi-square, I^2)?**
8. **An assessment of publication bias should include a combination of graphical aids (for example funnel plot, other available tests) and/or statistical tests (for example Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Noot 26: Non-HDL-cholesterol

Evidencetabellen

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Outcome measures and effect size	Comments
Boekholdt, 2012	Meta-analysis 8 onderzoeken (RCT'S) Sponsering: De meta-analyse is niet gesponserd. Alle geïncludeerde onderzoeken zijn gesponserd. De sponsors leverde de data voor de meta-analyse, maar hadden geen verdere betrokkenheid bij de meta-analyse. 16 van de 19 auteurs geven een mogelijke belangenverstrengeling aan. Doel van meta-analyse was het bepalen of bij patiënten behandeld met een statine het non-HDL een sterkere associatie heeft met HVZ dan LDL.	Inclusie criteria: • RCT • Behandeling met statine in minmaal 1 onderzoeksarm • Baseline meting en vervolgen van TC, LDL-C, HDL-C, TG en apoliproteine Exclusie criteria: • Mean follow-up < 2 jaar • N < 1000 patiënten N = 62.154 Mean leeftijd: 62,1 ± 8,9 jaar Sex: 75 % M / 25% V Patiënten (Placebo of lage dosis statine VERSUS (Hoge dosis) statine) 1. 2223/2221 2. 3301/3304	Non-HDL (formule TC minus HDL)	Mean follow-up: range 1,9 tot 6,1 jaar)	Eerste belangrijke hart-en vaatziekte **LDL** *1e quartile* Mean 1,3mmol/l Range < 1,6 mmol/l Event ratio 7,3% (697/9538) HR 1 (Referentie) *2e quartile* Mean 1,9 mmol/l Range 1,6-2,2 mmol/l Event ratio 14,2% (1360/9573) HR 1.06 (95%-BI: 0,97 tot 1,17) *3e quartile* Mean 2,5 mmol/l Range 2,2-2,8 mmol/l Event ratio 17,1% (1616/9478)	AMSTAR score 8 uit 11

	Geincludeerde RCT's 1. 4S P: Stabiele CHZ I: Placebo VS Simvastatin 20-40 mg 2. AFCAPS-TexCAPS P: Geen HVZ I: Placebo VS Lovastatin 20-40 mg 3. LIPID P. Stabiel CHZ I: Placebo VERSUS Pravastatin 40 mg 4. CARDS P: DM type 2 I: Placebo VERSUS Atorvastatin 10 mg 5. TNT *P:* Stabiel CHZ *I:* Atorvastatin 10 mg VERSUS Atorvastatin 80 mg 6. IDEAL P: Stabiel CHZ I: Simvastatin 20-40 mg versus Atorvastatin 80 mg 7. SPARCL P: CVA I: Placebo VERSUS Atorvastatin 80 mg 8. JUPITER P: Geen HVZ I: Placebo VERSUS Rosuvastatin 20 mg Primaire uitkomstmaat: Eerste belangrijke hart-en vaatziekte (MI, CHZ, AP, CVA)	3. 4502/4512 4. 1410/1428 5. 5006/4995 6. 4449/4439 7. 2365/2366 8. 8901/8901 Er zijn 38.153 patiënten geïcnludeerd in de meta-analyse, deze zijn behandeld met een statine en alle data was compleet (lost to follow-up 8%).			HR 1,15 (95%-BI: 1,05 tot 1,27) *4e quartile* Mean 3,3 mmol/l Range ≥ 2,8 mmol/l Event ratio 17,9% (1714/9564) HR 1,26 (95%-BI 1,14 tot 1,39) Lineare trend P < 0,001 Per 1 - Sd toename 1,13 (95%-BI 1,10 tot 1,17) P < 0,001 **Non-HDL** *1e quartile* Mean 1,78 mmol/l Range < 2,2 mmol/l Event ratio 7,3% (701/9659 HR 1 (Referentie) *2e quartile* Mean 2,5 mmol/l Range 2,2-2,9 mmol/l Event ratio 14.2% (1340/9404) HR 1,12 (95%-BI 1,02 tot 1,24) *3e quartile* Mean 3,2 mmol/l Range 2,9-3.5 mmol/l Event ratio 16.4% (1568/9564) HR 1.17 (95%-BI 1,06 tot 1,28) *4e quartile* Mean 4,2 mmol/l Range > 3,5 mmol/l Event ratio 18,7% (1778/9526) HR 1,42 (95%-BI 1,29 tot 1,56) Lineare trend P < 0,001	

					Per 1 - Sd toename 1,16 (95%-BI 1,12 tot 1,19) P < 0,001 Bootstrapanalyse tussen LDL en Non-HDL voor het verschil in voorspellen van HVZ per 1-SD toename is significant in het voordeel van Non-HDL. 1-sd toename is 0.9 mmol/L non-HDL Effect van statine op risico HVZ LDL Non-HDL HR (95%-BI) ≥ 2,6 ≥ 3,4 1,21 (1,13 tot 1,29) ≥ 2,6 < 3,4 1,02 (0,92 tot 1,12) < 2,6 ≥ 3,4 1,32 (1,17 tot 1,50) < 2,6 < 3,4 1,00 (Referentie)	

GRADE beoordeling kwaliteit systematische reviews

Onderzoek	Risico op bias	Inconsistentie	Indirectheid	Onprecies	Publicatie bias	Oordeel
Boekholdt, 2012	Laag	Afwezig	Ja[1]	Niet	Afwezig	Redelijke kwaliteit van bewijs

1. De geïncludeerde onderzoeken in de meta-analyse hadden niet als primaire eindpunt het onderzoeken van de associatie tussen LDL-C en non-HDL-C en welke streefwaarden van LDL-C en non-HDL-C overeenkomen.

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
PCSK9-inhibtors							
Schmidt, 2017 (individual study characteristics deduced from Schmidt, 2017) PS. Study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of RCTs *Literature search up to May 2016* **A**: Ballantyrne, 2015 **B**: Descartes **D**: FOURIER **H**: ODYSSEY COMBO I **I**: ODYSSEY COMBO II **J**: ODESSEY FH I **K**: ODESSEY FH II **M**: ODYSSEY Long Term **N**: ODYSSEY MONO **O**: ODYSSEY OPTIONS I **P**: ODYSSEY OPTIONS II **Q**: OSLER 1/2 **R**: OSLER-1 **S**: SPIRE 1/2 <u>Study design</u>: All were RCTs <u>Setting</u>: For all: outpatient care <u>Source of funding:</u> All RCTs were funded by pharmaceutical companies.	Inclusion criteria SR: • Parallel-group and factorial RCTs with follow-up of at least 24 weeks • Included adults 18 years of age or older, with or without a prior history of CVD • Randomised to a PCSK9 inhibitor or to placebo, statin, ezetimib of combination of these. Exclusion criteria SR: • Cluster RCTs, cross-over trails and non-randomised studies *20 studies included, of which five studies were only published as conference abstracts. These*	**A**: Bococizumab **B**: Evolocumab **D**: Evolocumab **H**: Alirocumab **I**: Alirocumab **J**: Alirocumab **K**: Alirocumab **M**: Alirocumab **N**: Alirocumab **O**: Alirocumab **P**: Alirocumab **Q**: Evolocumab **R**: Evolocumab **S**: Bococizumab Background therapy: **A**: Statin therapy **B**: Standard of care (Diet only, daily atorvastatin +/- ezetimib) **D**: Statin therapy	**A**: Placebo **B**: Placebo **D**: Placebo **H**: Placebo **I**: Ezetimib **J**: Placebo **K**: Placebo **M**: Placebo **N**: Ezetimib **O**: Ezetimib **P**: Ezetimib **Q**: Standard of care **R**: Standard of care **S**: Placebo	<u>End-point of follow-up</u>: **A**: 24 weeks **B**: 52 weeks **D**: 157 weeks **H**: 52 weeks **I**: 104 weeks **J**: 78 weeks **K**: 52 weeks **M**: 78 weeks **N**: 24 weeks **O**: 24 weeks **P**: 24 weeks **Q**: 52/48 weeks **R**: 52 weeks **S**: 143 weeks <u>For how many participants were no complete outcome data available?</u> (intervention/control) **A:** NA **B**: 134 **D**: Unclear **H**: 30 **I**: 13 **J**: 1 **K**: 2 **M**: 247 **N**: 0 **O**: 10 **P**: 7	<u>Outcome measure-1</u> Defined as LDL *Six months – compared with placebo* Pooled effect (random effects model): mean difference -58,73% (95%-CI -60,80 to -56,67) favoring PCSK9 inhibitors Heterogeneity (I^2): 88,1% *One year – compared with placebo* Pooled effect (random effects model): mean difference -52,87% (95%-CI -60,03 to -45,72) favoring PCSK9 inhibitors	<u>Facultative</u>: Brief description of author's conclusion Personal remarks on study quality, conclusions, and other issues (potentially) relevant to the research question Level of evidence: GRADE (per comparison and outcome measure) including reasons for down/upgrading Sensitivity analyses (excluding small studies; excluding studies with short follow-up; excluding low quality studies; relevant subgroup-analyses); mention only analyses which are of potential importance to the research question

		studies were excluded. <u>Important patient characteristics at baseline</u>: <u>N, mean age</u> **A**: 354 patients, 59 (SD 11) yrs **B**: 905 patients, 56 (SD 11) yrs **D**: 27564 patients, 63 (SD 9) yrs **H**: 316 patients, 63 (SD 9) yrs **I**: 720 patients, 62 (SD 9) yrs **J**: 486 patients, 52 (SD 13) yrs **K**: 249 patients, 53 (SD 17) yrs **M**:2341 patients, 63 (SD 11) yrs **N**: 103 patients, 60 (SD 5) yrs **O**: 355 patients, 63 (SD 10) yrs **P**: 305 patients, 61 (SD 10) yrs	**H**: Maximal tolerated dose of statin **I**: Maximal tolerated dose of statin **J**: Maximal tolerated dose of statin and possible of other lipid-lowering therapies **K**: Maximal tolerated dose of statin and possible of other lipid-lowering therapies **M**: Standard of care **N**: Diet **O**: 24 weeks 20 or 40 mg of baseline atorvastatin and diet **P**: 24 weeks 10 or 20 mg of baseline rosuvastatin and diet		**Q**: 738 **R**: 169 **S**: Unclear	*Six months – compared with ezetimib or statin* Pooled effect (random effects model): mean difference -54,13% (95%-CI -55,95 to -52,32) favoring PCSK9 inhibitors Heterogeneity (I^2): 98,0% <u>Outcome measure-2</u> Defined as CVD *Compared with placebo* Pooled effect (fixed effects model): OR 0,86 (95%-CI 0,80 to 0,92) favoring PCSK9 inhibitors Heterogeneity (I^2): not reported	Heterogeneity: clinical and statistical heterogeneity; explained versus unexplained (subgroupanalysis) S: Many participants were lost to follow-up due to antidrug antibody response

		Q: 4465 patients, 58 (SD 11) yrs **R**: 1104 patients, 56 (SD 12) yrs **S**: 27438 patients, 63 (SD 9) yrs <u>Sex</u>: **A**: 49% Male **B**: 49% Male **D**: 75% Male **H**: 66% Male **I**: 74% Male **J**: 56% Male **K**: 53% Male **M**: 62% Male **N**: 53% Male **O**: 65% Male **P**: 61% Male **Q**: 51% Male **R**: 45% Male **S**: 70% Male <u>History of CVD:</u> **A:** NA **B**: 136 (15%) **D**: 27564 (100%) **H**: 247 (78%) **I**: 649 (90%) **J**: 225 (46%) **K**: 89 (36%)	**Q**: Standard of care **R**: Standard of care **S**: Statins and/or ezetimib			<u>Outcome measure-3</u> Defined as mortality due to CVD Not reported <u>Outcome measure-4</u> Defined as adverse events *Compared with placebo* Pooled effect (fixed effects model): OR 1,08 (95%-CI 1,04 to 1,12) favoring placebo Heterogeneity (I^2): not reported *Compared with ezetimib and statin* Pooled effect (fixed effects model): OR	

		M: 1607 (68%) **N**: 103 (100%) **O**: 200 (56%) **P**: 177 (58%) **Q**: NA **R**: 210 (19%) **S**: 23198 (85%) <u>Participants with FH:</u> **A**: NA **B**: NA **D**: NA **H**: 0 **I**: 0 **J**: 485 (100%) **K**: 249 (100%) **M**: 415 (18%) **N**: 0 **O**: 31 (9%) **P**: 41 (13%) **Q**: NA **R**: 414 (38%) **S**: 1072 (4%)				1,18 (95%-CI 1,05 to 1,34) favoring Ezetimib and statins Heterogeneity (I^2): not reported	
Ezetimib							
Nuβbaumer, 2016 (individual study characteristics deduced from Nuβbaumer, 2016) PS. Study characteristics and	See the full article for all relevant information https://www-aerzteblatt-de.eur.idm.oclc.org/int/archive/article?id=180413						

results are extracted from the SR (unless stated otherwise)							

Noot 27: Behandeling lipiden

Evidencetabellen

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Schmidt, 2017	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes
Nuβbaumer, 2016	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	No	Yes

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined.**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched.**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons.**
4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported.**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs).**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, Risk of Bias table et cetera)**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (for example Chi-square, I^2)?**
8. **An assessment of publication bias should include a combination of graphical aids (for example funnel plot, other available tests) and/or statistical tests (for example Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Noot 28: Dyslipidemie bij (kwetsbare) ouderen

Evidencetabellen

Ouderen zonder hart- en vaatziekten

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison/ control (C)	Follow-up	Outcome measures and effect size	Comments
Elderly without cardiovascular diseases							
Teng, 2015	SR and meta-analyses of RCT's and subgroups of RCTs *Literature search up to August 2014* **A**: ALLHAT, 2002 **B**: Collier, 2011 **C**: Bruckert, 2003 **D**: Glynn, 2010 **E**: Stephard, 2002 Study design: RCT Setting and Country: **A**: US, Puerto Rico, US Virgin	Inclusion criteria SR: • Trials in Human and published in English • Participants ≥ 65 years. If participants < 65 years, inclusion when stratified results for patients >65 years were reported. • Participants without established cardiovascular disease • Comparison between statin and usual care/placebo • Outcomes included major adverse	**A**: Pravastatin, 40 mg/day **B**: Atorvastatin, 10mg/day **C**: Fluvastatin XL, 80 mg/day **D**: Rosuvastatin, 20 mg/day **E**: Pravastatin, 40 mg/day	**A**: placebo or usual care **B**: placebo or usual care **C**: placebo or usual care **D**: placebo or usual care **E**: placebo or usual care	End-point of follow-up: Mean follow-up: **A**: 4.8 years **B**: 3.3 years **C**: 1 years **D**: 1.9 years **E**: 3.2 years For how many participants were no complete outcome data available? (intervention/control) **A:** Not reported (low Risk of Bias) **B**: Not reported (low Risk of Bias) **C**: Not reported (low Risk of Bias) **D**: Not reported (low Risk of Bias) **E**: Not reported (low Risk of Bias)	1.Quality of life Not reported 2.Cognitive function Not reported 3.Adverse events Defined as myalgia **A**: Not reported **B**: RR 0,82 (95%-CI: 0,58;1,15) **C**: RR 0,11 (95%-CI: 0,01;2,12) **D**: RR 1,31 (95%-CI: 0,29;5,83) **E**: RR 1,15 (95%-CI: 0,71;1,84) Defined as new onset diabetes **A**: Not reported **B**: RR 0,9 (95%-CI: 0,64;1,26) **C**: Not reported **D**: RR 1,25 (95%-CI: 0,91;1,73)	Neil, 2006, Collins, 2003, Nakaya, 2011 were excluded because the age of the study sample was < 70 years. Of the original 8 RCTs included, 2 focussed on elderly, six trials comprised subgroups. Teng, 2015 judged the overall quality of evidence (8 RCTs) as moderate. A was open labelled, B, C, D and E were sponsored by the industry.

	Islands and Canada **B**: UK, Sweden, Norway, Denmark, Finland, Ireland **C**: France, Italy, Spain, Belgium and Israel **D**: North America, South America, Europe and Africa **E**: Scotland, Ireland and The Netherlands <u>Source of funding:</u> Systematic review: Not sponsored **A**: not sponsored by industry **B**: Sponsored by industry **C**: Sponsored by industry **D**: Sponsored by industry **E**: Sponsored by industry	cardiovascular events, all-cause mortality, elevation in hepatic transaminases, elevation in creatine kinase, myalgia, myopathy, rhabdomyolysis, serious adverse events, tolerability, incidence of new-onset diabetes and/or cognitive impairment. Exclusion criteria SR: • None. *8 studies included, of which 5 had a study sample with a age > 70 years* <u>Important patient</u>				**E**: Not reported Defined as serious adverse events **A**: RR 0,88 (95%-CI: 0,45;1,73) **B**: RR 0,96 (95%-CI: 0,87;1,06) **C**: RR 2,05 (95%-CI: 0,19;22,54) **D**: RR 1,04 (95%-CI: 0,94;1,15) **E**: RR 1,01 (95%-CI: 0,96;1,06) 4.<u>Mortality</u> Defined as all-cause mortality **A**: RR 1,01 (95%-CI: 0,91;1,13) **B**: RR 0,97 (95%-CI: 0,77;1,22) **C**: RR 1,02 (95%-CI: 0,06; 16,35) **D**: 0,79 (95%-CI: 0,62;1,02) **E**: 0,98 (95%-CI: 0,88;1,04) 5.<u>CVD events</u> Defined as major adverse cardiovascular events (myocardial infarction, stroke, coronary	

		characteristics at baseline: N, mean age **A**: 5809 patients, 72 yrs **B**: 4445 patients, 71 yrs **C**: 1229 patients, 75.5 yrs **D:** 5695 patients, 74 yrs **E:** 3239 patients, 75 yrs *Sex:* **A**: 52,2% Male **B**: 81,4% Male **C**: 25,1% Male **D:** 48,4% Male **E:** 41,5% Male *Diabetes:* **A**: 38,3% **B**: 100% **C**: 7% **D:** 0% **E:** 12,2% *Hypertension* **A**: 100% **B**: 26,7% **C**: 55,9%				revascularization, cardiac sudden death, angina) **A**: RR 0,96 (95%-CI: 0,89;1,05) **B**: RR 0,82 (95%-CI: 0,73;0,93) **C**: Not reported **D**: 0,62 (95%-CI: 0,46;0,82) **E**: 0,94 (95%-CI: 0,78;1,14) Defined as myocardial infarction **A**: RR 0,81 (95%-CI: 0,67;0,99) **B**: RR 0,63 (95%-CI: 0,45;0.89) **C**: Not reported **D**: 0,68 (95%-CI: 0,45;1,02) **E**: 0,91 (95%-CI: 0,72;1,14) Defined as stroke **A**: RR 0,98 (95%-CI: 0,79;1,20) **B**: RR 0,80 (95%-CI: 0,58;1,11) **C**: Not reported **D**: Not reported **E**: 1,03 (95%-CI: 0,73;1,45)	

		D: 65,6% **E:** 71,6% Groups comparable at baseline? Unclear					

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons**
4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs)**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, Risk of Bias table etc.)**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (e.g. Chi-square, I^2)?**
8. **An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Study **First author, year**	**Appropriate and clearly focused question?[1]** **Yes/no/unclear**	**Comprehensive and systematic literature search?[2]** **Yes/no/unclear**	**Description of included and excluded studies?[3]** **Yes/no/unclear**	**Description of relevant characteristics of included studies?[4]** **Yes/no/unclear**	**Appropriate adjustment for potential confounders in observational studies?[5]** **Yes/no/unclear/notapplicable**	**Assessment of scientific quality of included studies?[6]** **Yes/no/unclear**	**Enough similarities between studies to make combining them reasonable?[7]** **Yes/no/unclear**	**Potential risk of publication bias taken into account?[8]** **Yes/no/unclear**	**Potential conflicts of interest reported?[9]** **Yes/no/unclear**
Teng, 2015	Yes	No	No	No, some of the data could not be retrieved	Not appliciable	Yes	Yes	No	yes

Ouderen met hart- en vaatziekten

Study reference	**Study characteristics**	**Patient characteristics [2]**	**Intervention (I)**	**Comparison/ control (C) [3]**	**Follow-up**	**Outcome measures and effect size [4]**	**Comments**

Elderly with cardiovascular diseases							
Shepherd, 2002 Trompet, 2010	Type of study: RCT Setting: multicenter Country: Scotland, Ireland and The Netherlands Source of funding: Industry sponsored	Inclusion criteria: • Aged between 70-82 years • Pre-existing vascular disease or raised risk of such disease because of smoking, hypertention, or diabetes • Total plasma cholesterol between 4,0-9,0 mmol/L • Triglyceride concentratie < 6,0 mmol/L • Usage of > 75% and < 120% of placebo medication during 4-week single-blind placebo lead-in period. Exclusion criteria: • Poor cognitive function (mini mental state examination score < 24)	Pravastatin 40mg/day	Placebo	Length of follow-up: Shepherd, 2002: 3,2 years (range 2,8 to 4,0 years) Trompet, 2010: mean 42 months (range 36 to 48 months) Loss to follow-up: Not specified for patients with previous vascular disease. Incomplete outcome data: Likely all patients analysed.	1.Quality of life Not reported 2.Cognitive function Determined using the Mini-Mental State Examination (MMSE). Analyses were adjusted for age, educational status, country and when appropriate for sex and version of the test. Four tests were included: 1. Attention (Executive functioning, Stroop-Colour-Word-test) Est 0,36 (95%-CI=-0,02;0,74) 2. Processing Speed (Executive functioning, Letter-Digit Coding Test) Est -0,02 (95%-CI=-0,08;0,09) 3. Immediate recal (Memory, 15-Picture Learning test) Est 0,002 (95%-CI=-0,03;0,04)	408 patients of the entire cohort (primary and secondary prevention), 277 control patients and 131 patients from the intervention group used non-study statin therapy. Here, we report only the results of the subgroup analyses that included patients with stable angina, intermittend claudication, stroke, transient ischeamic attack, myocardial infarction, arterial surgery or amputation for vascular disease more than 6 months before study entry.

		N total at baseline: Intervention: 1306 Control:1259 Important prognostic factors: Data only reported for the complete cohort (primary and secondary prevention combined) Groups comparable at baseline? Unknown				4. Delayed recal (Memory, 15-Picture Learning test) Est 0,04 (95%-CI=-0,01;0,09) 3.Adverse events Not reported separately for subgroup of patients with previous vascular disease. 4.Mortality (all-cause and CVD) Not reported separately for subgroup of patients with previous vascular disease. 5.CVD events Defined as definite or suspect death from coronary heart disease, non-fatal myocardial infarction, and fatal or non-fatal stroke I: 227 (17,4%) C: 273 (21,7%) HR 0,78 (95%-CI=0,66;0,93)	

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders)**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls**

4. For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders

Study reference (first author, publication year)	**Describe method of randomisation[1]**	**Bias due to inadequate concealment of allocation?[2]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?[4]** (unlikely/likely/unclear)	**Bias due to loss to follow-up?[5]** (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?[6]** (unlikely/likely/unclear)
Shepherd, 2002 Trompet, 2015	"Sequence was generated with a computerised pseudorandom number generator and consisted of balanced blocks of size four"	Unlikely	Unlikely	unlikely	unlikely	Unlikely	Unclear	Unlikely

1. **Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.**
2. **Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules.**
3. **Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignment influences the process of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**

4. **Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.**
5. **If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the Risk of Bias is unclear**
6. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the Risk of Bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

Noot 29: Bloeddrukmeting

Evidencetabellen

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Bos, 2017	Type of study: Cross-sectional study Setting: All consecutive patients who underwent OBP30 for medical reasons over a 6-month period in a single primary health care center Country: The Netherlands	Inclusion criteria: • Consecutive patients undergoing OBP30 Exclusion criteria: • Change in medication between last recorded OBP reading and subsequent OBP30 and previous OBP30 during the study period N total at baseline: 207 patients Important prognostic factors[2]:	BP30 BP30 is performed with the patient sitting alone and undisturbed for 30 minutes while the blood pressure is measured automatically every 5 minutes, producing 7 readings. The resulting OBP30 is the mean of the last 6 blood pressure readings.	OBPM	Length of follow-up: Not applicable because of the cross-sectional design Loss-to-follow-up: N = 6 (3%) Reasons (n = 2 missing OBP; n = 2 technical problems OBP30; n = 2 Start of medication between OBP and OBP30) Incomplete outcome data: N = 6 (3%) Reasons (n = 2 missing OBP; n = 2 technical problems OBP30; n = 2 Start of medication	Outcome Blood pressure *Systolic blood pressure (mmHg, 95%-CI)* BP30: 140,9 (138,4 to 143,5) OBPM: 163,8 (161,5 to 166,2) MD: -22,8 (-26,1 to -19,8) *Diastolic blood pressure (mmHg, 95%-CI)* BP30: 77,3 (75,7 to 78,9) OBPM: 88,9 (87,4 to 90,4) MD: -11,6 (-13,1 to -10,2)	Authors' conclusions: BP30 yields considerably lower blood pressure readings than OBPM in all studied patient groups. BP30 is a promising technique to reduce overtreatment of white-coat hypertension in primary health care.

	Source of funding: None received	Mean age: 68 (SD 13) Sex: 43% Male CVD: 20% Diabetes: 20%			between OBP and OBP30)		
Scherpbier, 2011	Type of study: Cross-sectional study Setting: General practices Country: The Netherlands Funding: This study was not funded	<u>Inclusion criteria</u>: • Consecutive patients who attended the practice with a main reason for encounter that warranted blood pressure measurement <u>Exclusion criteria</u>: • Atrial fibrillation • Documented heart valve disease • Complete axllary lymph node excision on the right side • Upper arm circumference more than 35 cm. <u>N total at baseline</u>: 105 patients (83 patients were described) <u>Important prognostic factors</u>[2]:	BP30 30-minute OBPM of 11 measurements, of which 10 were made in the absence of the researcher. The position of the patient and cuff were not altered. The first measurement was discarded.	Standardised OBPM After a 5-minute rest period in the absence of the observer, three readings were taken. The first measurement was discarded.	<u>Length of follow-up</u>: Not applicable because of the cross-sectional design <u>Loss-to-follow-up</u>: N = 22 of 105 patients (21%) Reasons (n = 10 because of fewer than nine measurements of BP30 were valid; 6 because of medication between the two visits, two because the felt unwell during the measurements, two because they altered the position of their arm during measurements, and two because they were unable to come for the second visit). <u>Incomplete outcome data</u>:	<u>Outcome Blood pressure</u> *Systolic blood pressure (mmHg, SD))* BP30: 126,8 (14,1) OBPM: 134,4 (16,4) MD: -7,6 (-9,1 to -6,1) *Diastolic blood pressure (mmHg, 95%-CI)* BP30: 81,6 (10,1) OBPM: 84,1 (10,8) MD: -2,5 (-3,4 to -1,5)	Authors' conclusions: Thirty-minute OBPM resulted in lower readings than standardised OBPM and had a better repeatability. These results suggest that 30-minute OBPM better reflects the patient's true blood pressure than standardised OBPM does.

		Mean age: 62 (SD 11) Sex: 39% Male			N = 22 of 105 patients (21%) Reasons (n = 10 because of fewer than nine measurements of BP30 were valid; 6 because of medication between the two visits, two because the felt unwell during the measurements, two because they altered the position of their arm during measurements, and two because they were unable to come for the second visit).		
Van der Wel, 2011	Type of study: Cross-sectional study Setting: All patients referred by their family physician Country: The Netherlands Funding: Non-commercial	<u>Inclusion criteria</u>: • Aged 18 years or older • Referred by family physician <u>Exclusion criteria</u>: • Known atrial fibrillation • Irregular pulse • Pregnancy • Night shift work <u>N total at baseline</u>: 96 patients	BP30 Defined as 30-minute OBPM to be the mean blood pressure calculated from the 6 measurements taken at 5-minute intervals from t = 5 to t = 30 minutes.	24-hour ABPM The 24-hour ABPM was set at 20-minute intervals from 7 AM to 11 PM and at 1-hour intervals from 11 PM to 7 AM. Blood pressure was monitored on the same arm as during the 30-minute OBPM. Patients	<u>Length of follow-up</u>: Not applicable because of the cross-sectional design <u>Loss-to-follow-up</u>: N = 12 (13%) Reasons (n = 6 measurements exceeded the predefined number of erroneous readings; in 5 patients a problem occurred with cuff fitting during the 24-hour ABPM, and 1	<u>Outcome Blood pressure</u> *Systolic blood pressure (mmHg, SD)* BP30: 141 (17) Daytime ABPM: 141 (14) MD: 0 (-2 to 2) *Diastolic blood pressure (mmHg, SD)* BP30: 84 (11) Daytime ABPM: 82 (11) MD: 2 (0 to 3)	Authors' conclusions: The 30-minute OBPM appears to agree well with daytime ABPM and has the potential to detect white-coat and masked hypertension. This finding makes 30-minute OBPM a promising new method to determine blood pressure during diagnosis and follow-up of patients with elevated blood pressure.

		Important prognostic factors[2]: Mean age: 57 (SD 20) Sex: 39% Male		were instructed to perform their usual daily activities but to stop moving and be silent during measurements. The mean daytime ABPM was calculated from the readings of 9 AM to 9 PM.	patient was disturbed during the 30-minute OBPM). Incomplete outcome data: N = 12 (13%) Reasons (n = 6 measurements exceeded the predefined number of erroneous readings; in 5 patients a problem occurred with cuff fitting during the 24-hour ABPM, and 1 patient was disturbed during the 30-minute OBPM).		
Culleton, 2006	Type of study: Cross-sectional study Setting: Adult hypertensive patients refer for ABPM. Country: Canada Funding: Commercial	Inclusion criteria: • Aged 18 years or older • Referred by family physician Exclusion criteria: • Usual clinic blood pressure readings < 140 mm Hg systolic and < 90 mm Hg diastolic • Incomplete or invalid 24-h ABPM recordings	BP30 A 5-min rest in a quiet comfortable room was used prior to measurement. All blood pressure measurements were obtained with the patient in a sitting position with the arm supported. The BpTRU device was set to measure blood pressure immediately and every 5 min for 25 min. The mean	24-hour ABPM The mean daytime ABPM systolic and diastolic pressures were used as the reference standard. Daytime was defined according to each patient's	Length of follow-up: Not applicable because of the cross-sectional design Loss-to-follow-up: Not stated Incomplete outcome data: Not stated	Outcome Blood pressure PB30 versus 24-ABPM *Systolic blood pressure (mmHg, SD)* OBP30: 132,1 (16,8) Daytime ABPM: 141,8 (13) MD: -9,7 (-12,1 to -7,2) *Diastolic blood pressure (mmHg, SD)* BP30: 81,5 (9,5)	Authors' conclusions: Although BpTRU reduces white-coat effect and white-coat hypertension, blood pressure is underestimated by the device, leading to misclassification of hypertension. BpTRU, when set at 5-min blood pressure measurement intervals, should not be used in clinical practice.

		N total at baseline: 107 patients Important prognostic factors[2]: Mean age: 57 (SD 12) Sex: 47% Male	of the last five BpTRU measurements were used for all analyses.	waking hours as noted in the patient's diary.		Daytime ABPM: 85,3 (9,1) MD: -3,9 (-5,3 to -2,4)	

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures.**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders).**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls.**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders.**

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?[1]** (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?[2]** (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?[3]** (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?[4]** (unlikely/likely/unclear)
Bos, 2017	Unlikely. A consecutive sample of patients was used.	Not applicable	Likely. Not clearly described how OBP was obtained.	Unlikely. No need for adjustment for prognostic factors.
Scherpbier, 2011	Unlikely. A consecutive sample of patients was used.	Not applicable	Unlikely. Both blood pressure measures were described in detail.	Unlikely. No need for adjustment for prognostic factors.
Van der Wel, 2011	Unlikely. A consecutive sample of patients was used.	Not applicable	Unlikely. Both blood pressure measures were described in detail.	Unlikely. No need for adjustment for prognostic factors.
Culleton, 2006	Unclear. Patients referred to centre for ABPM, unclear whether this were consecutive patients.	Not applicable	Unlikely. Both blood pressure measures were described in detail.	Unlikely. No need for adjustment for prognostic factors.

1. **Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.**

2. **2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The Risk of Bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.**
3. **Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.**

Noot 34: Bloeddrukstreefwaarde bij behandeling hypertensie bij (kwetsbare) ouderen (> 70 jaar)

Evidencetabellen

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison/ control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Comparison: Antihypertensive versus placebo							
Beckett, 2008 Additional data from Peters, 2008	Type of study: RCT (parallel) Setting: 195 centers Country: 13 countries across Western and Eastern Europe, China, Australasia, and North Africa Source of funding: Non-commercial	Inclusion criteria: • 80 years or older • Persistent hypertension (a sustained systolic hypertension of 160 mmHg) Exclusion criteria: • Contraindication to use the trial medications • Accelerated hypertension • Secondary hypertension • Hemorrhagic stroke in the previous 6 months • Heart failure requiring treatment with antihypertensive medication	Indapamide (sustained release, 1,5 mg) The angiotensin-converting-enzyme inhibitor perindopril (2 or 4 mg), or matching placebo, was added if necessary to achieve the target blood pressure of 150/80 mmHg.	Matching placebo	Length of follow-up: Mean 2,1 years (range 0 to 6,5) Loss-to-follow-up: Intervention: N = 847 (44%) Reasons: 196 died; 282 declined to participate; 4 were withdrawn by investigator; 27 had protocol withdrawal event and no open follow-up; 164 were at centers closed by data monitoring committee; 168 for other administrative reasons; 6 lost to follow-up	1. Quality of life Not reported 2. Functional status Cognition, measured with the MMSE*, mean change from baseline I: 0,7 points (SD 4,0) C: -1,1 points (SD 3,9) P = 0,08 Dementia, n I: 126 C: 137 HR 0,86 (95%-CI: 0,67-1,09) 3. Adverse events	Data on cognition was reported in the publication by Peters, 2008. *Data was available in 1687 under active treatment versus 1649 under placebo.

		• Serum creatinine level greater than 150 µmol per liter • Serum potassium level of less than 3,5 mmol per liter or more than 5,5 mmol per liter • Gout • Diagnosis of clinical dementia • Requirement of nursing care <u>N total at baseline</u>: Intervention: 1933 Control: 1912 <u>Important prognostic factors</u>[2]: Age ± SD: I: 83 (3) C: 83 (3) Sex: I: 39% M C: 40% M Groups comparable at baseline? Yes			Control: N = 896 (47%) Reasons: 235 died; 266 declined to participate; 5 were withdrawn by investigator; 42 had protocol withdrawal event and no open follow-up; 166 were at centers closed by data monitoring committee; 171 for other administrative reasons; 11 lost to follow-up <u>Incomplete outcome data</u>: Intervention: N = 847 (44%) Reasons: 196 died; 282 declined to participate; 4 were withdrawn by investigator; 27 had protocol withdrawal event and no open follow-up; 164 were at centers closed by data monitoring committee; 168 for other administrative	Number of serious adverse events, n (%) I: 358 (19) C: 448 (23) P = 0,001 4. <u>Mortality</u> Measured as all-cause mortality or death due to a cardiovascular event, n (rate per 1000 patient years) *Total mortality, hazard ratio* I: 196 (47) C: 235 (60) HR 0,79 (95%-CI 0,65-0,95) *Death due to cardiovascular event, hazard ratio* I: 99 (24) C: 121 (31) HR 0,77 (95%-CI 0,60-1,01) 5. <u>CVD</u> Measured as all cardiovascular	

					reasons; 6 lost to follow-up Control: N = 896 (47%) Reasons: 235 died; 266 declined to participate; 5 were withdrawn by investigator; 42 had protocol withdrawal event and no open follow-up; 166 were at centers closed by data monitoring committee; 171 for other administrative reasons; 11 lost to follow-up	events, n (rate per 1000 patient years) I: 138 (34) C: 193 (51) HR 0,66 (95%-CI 0,53-0,82) 6. <u>Blood pressure</u> Blood pressure was measured annual, mean change from baseline in BP (SD) in mmHg *At two years, seated* I: SBP 29,5 (15,4); DBP 12,9 (9,5) C: SBP 14,5 (18,5); DBP 6,8 (10,5)	
Staessen, 1998	Type of study: RCT (parallel) Setting: Patients with isolated systolic hypertension Country: Belgium, Belorussia, Bulgaria,	<u>Inclusion criteria</u>: • 60 years or older • During run-in placebo phase, seated systolic blood pressure between 160 and 219 mmHg and diastolic blood pressure below 95 mmHg • Standing systolic blood pressure of 140 mmHg of more	Antihypertensive treatment – Nitrendipine (10-40 mg/d) If necessary, the calcium channel blocker was combined with or replaced by enalapril maleate (5-20 mg/d) or hydrochlorothiazide (12,5-25 mg/d) or both drugs. The study medications were stepwise titrated and	Control group – matching placebo	<u>Length of follow-up</u>: Median follow-up of 2.0 years (range 1 to 97 months) <u>Loss-to-follow-up</u>: Intervention: N = 660 (28%) Reasons: 123 died; 174 supervised open follow-up; 242 unsupervised open follow-up; 121	1. <u>Quality of life</u> Not reported 2. <u>Functional status</u> Not reported 3. <u>Adverse events</u> Not reported 4. <u>Mortality</u> Measured as all-cause mortality or death due to a	

	Croatia, Estonia, Finland, France, Germany, Greece, Ireland, Israel, Italy, Lithuania, Netherlands, Poland, Portugal, Romania, Russian Federation, Slovakia, Slovenia, Spain, United Kingdom Source of funding: Industry	• Consented to be enrolled • Long-term follow-up was possible <u>Exclusion criteria</u>: • Systolic hypertension secondary to a disorder that needed specific medical or surgical treatment • Retinal haemorrhage or papilledema • Congestive heart failure • Dissecting aortic aneurysm • Serum creatinine at presentation of 180 µmol/ L or more • History of severe nosebleeds, stroke, myocardial infarction in the year before the study • Dementia or substance abuse • Any condition prohibiting a sitting or standing position • Severe concomitant	combined to reduce sitting systolic blood pressure by 20 mmHg or more to less than 150 mmHg.		unavailable for follow-up Control: N = 780 (34%) Reasons: 137 died; 295 supervised open follow-up; 232 unsupervised open follow-up; 116 unavailable for follow-up <u>Incomplete outcome data</u>: Intervention: N = 660 (28%) Reasons: 123 died; 174 supervised open follow-up; 242 unsupervised open follow-up; 121 unavailable for follow-up Control: N = 780 (34%) Reasons: 137 died; 295 supervised open follow-up; 232 unsupervised open follow-up; 116 unavailable for follow-up	cardiovascular event, n (rate per 1000 patient years) *Total mortality, hazard ratio* I: 123 (20,5) C: 137 (24) HR 0,86 (95%-CI 0,67-1,10) *Death due to cardiovascular event, hazard ratio* I: 59 (9,8) C: 77 (13,5) HR 0,73 (95%-CI 0,52-1,03) 5. <u>CVD</u> Measured as all cardiovascular events, n (rate per 1000 patient years) I: 137 (23,3) C: 186 (33,9) HR 0,69 (95%-CI 0,55-0,86) 6. <u>Blood pressure</u> Blood pressure was measured every three months, mean	

		cardiovascular or noncardiovascular disease N total at baseline: Intervention: 2398 Control: 2297 Important prognostic factors[2]: Age ± SD: 70,2 (6,7) Sex: 33% M Groups comparable at baseline? Cannot be judged				change from baseline in BP (SD) in mmHg *At median follow-up, seated* I: SBP 23 (16); DBP 7 (8) C: SBP 13 (17); DBP 2 (8) Mean difference SBP: 10.1 (95CI: 8.8-11.4) Mean difference DBP: 4,5 (95%-CI: 3,9-5,1)	
Comparison: intensive treatment versus standard treatment							
Wei, 2013	Type of study: RCT (parallel) Setting: Hypertensive patients Country: China Source of funding: Not stated	Inclusion criteria: • Older than 70 years • SBP ≥ 150 mmHg and /or DBP ≥ mmHg, measured twice on different days OR diagnosed with hypertension and currently receiving antihypertensive treatment. Exclusion criteria: • Secondary hypertension	Intensive treatment (blood pressure target ≤140/90 mmHg)	Standard treatment (blood pressure target ≤150/90 mmHg)	Length of follow-up: 4 years Loss to follow-up: Intervention: N = 2 (0,6%) Reasons: 1 consent withdrawal; 1 lost to follow-up Control: N = 7 (2%) Reasons: 5 consent withdrawal; 2 lost to follow-up	1. Quality of life Not reported 2. Functional status Not reported 3. Adverse events Not reported 4. Mortality Measured as all-cause mortality or death due to a cardiovascular event, n (%)	Patients were examined on at least two separate occasions, and BP was measured on the right upper arm at least twice per visit by the auscultatory method using a sphygmomanometer with the patients in the sitting position after 5 to 10 minutes of rest. If measured values differed by > 4 mmHg, recalibration

		• Valvular heart disease • Chronic kidney dysfunction • Previous myocardial infarction • Stroke in the past six months <u>N total at baseline</u>: Intervention: 363 Control: 361 <u>Important prognostic factors</u>[2]: Age ± SD: I: 76 (5) C: 76 (5) Sex: I: 67% M C: 66% M Groups comparable at baseline? Yes			<u>Incomplete outcome data</u>: Intervention: N = 2 (0,6%) Reasons: 1 consent withdrawal; 1 lost to follow-up Control: N = 7 (2%) Reasons: 5 consent withdrawal; 2 lost to follow-up	*Total mortality, risk ratio* I: 51 (14) C: 87 (24) RR 0,63 (95%-CI 0,46-0,87) *Death due to cardiovascular event, risk ratio* I: 25 (7) C: 50 (14) RR 0,53 (95%-CI 0,33-0,84) 5. <u>CVD</u> Measured as all cardiovascular events, n (%) I: 40 (11) C: 67 (19) RR 0,63 (95%-CI 0,44-0,92) 6. <u>Blood pressure</u> Blood pressure was measured every six months, mean BP (SD) in mmHg I: SBP 135,7 (9,0); DBP 76,2 (6,1)	was required. BP measurements were performed at 8 AM to 11 AM and averaged for each visit. BP was monitored after enrollment, which was measured in the fourth week, the third month, the sixth month, and every 6 months thereafter. By the end of the study, all patients were followed-up an average of 10 times.

						C: SBP 149,7 (11,0); DBP 82,1 (7,5) Mean difference SBP 14; DBP 6, p < 0,01)	
Ogihara, 2010	Type of study: RCT (parallel) Setting: Elderly with isolated systolic hypertension Country: Japan Source of funding: Non-commercial	Inclusion criteria: • Aged between 70 and 84 years • Isolated systolic hypertension (systolic BP > 160 mmHg and diastolic BP < 90 mmHg) N total at baseline: Intervention: 1627 (1545 described) Control: 1633 (1534 described) Important prognostic factors[2]: Age ± SD: I: 76 (4) C: 76 (4) Sex: I: 38% M C: 37% M Groups comparable at baseline? Yes	Strict control group Valsartan, 40 to 80 mg once daily, was administrated as the first-step therapy. If the target BP in each group was not achieved within 1 to 2 months, the dose of valsartan was increased ≤160 mg, and/or other antihypertensive agents except other angiotensin II type 1 receptor blockers were added, for example, low-dose diuretics, Ca antagonists, and so on to maintain the target BP.	Moderate control group	Length of follow-up: Mean 2,85 years Loss-to-follow-up: Intervention: N = 82 (5%) Reasons: 42 withdrew consent; 40 no follow-up just after randomization Control: N = 99 (6%) Reasons: 45 withdrew consent; 54 no follow-up just after randomization Incomplete outcome data: Intervention: N = 82 (5%) Reasons: 42 withdrew consent; 40 no follow-up just after randomization Control: N = 99 (6%)	1. Quality of life Not reported 2. Functional status Not reported 3. Adverse events Measured as the rates of serious adverse events, percentage I: 5,6% C: 5,2% P = 0,61 4. Mortality Measured as all-cause mortality or death due to a cardiovascular event, n (%) *Total mortality, hazard ratio* I: 24 (2) C: 30 (2) HR 0,78 (95%-CI 0,46-1,33), adjusted for sex, age, BMI,	About 50% in each group were already taking antihypertensive drugs.

					Reasons: 45 withdrew consent; 54 no follow-up just after randomization	smoking, dyslipidaemia, diabetes mellitus, and antihypertensive agents used before enrolment. *Death due to cardiovascular event, hazard ratio* I: 11 (1) C: 11 (1) HR 0,97 (95%-CI 0,42-2,25), adjusted for sex, age, BMI, smoking, dyslipidaemia, diabetes mellitus, and antihypertensive agents used before enrolment. 5. <u>CVD</u> Not reported 6. <u>Blood pressure</u> Blood pressure at the end of 36 months, mean BP (SD) in mmHg I: SBP 136,6 (13,3); DBP 74,2 (8,8)	

						C: SBP 142,0 (12,5); DBP 76,5 (8,9) Mean difference SBP 5,6; DBP 1,7, p < 0,001)	
The SPRINT research group, 2015	Type of study: RCT (parallel) Setting: Patients at increased risk of CVD Country: United States of America Source of funding: Non-commercial	<u>Inclusion criteria</u>: • Age at least 50 years • Systolic BP of 130 to 180 mmHg • Increased risk of CVD* <u>Exclusion criteria</u>: • Diabetes mellitus • Prior stroke <u>N total at baseline</u>: Intervention: 4678 (1317 older than 74 yrs) Control: 4683 (1319 older than 74 yrs) <u>Important prognostic factors</u>[2]: Age ± SD: I: 79 (4) C: 79 (4) Sex: Not stated for the subgroup	Intensive treatment (blood-pressure target less than 120 mmHg)	Standard treatment (blood-pressure target less than 140 mmHg)	<u>Length of follow-up</u>: Median follow-up: 3,26 (not stated for the subgroup) <u>Loss-to-follow-up</u>: Not stated for the subgroup <u>Incomplete outcome data</u>: Not stated for the subgroup	1. <u>Quality of life</u> Not reported 2. <u>Functional status</u> Not reported 3. <u>Adverse events</u> Measured as the rates of serious adverse events**, n (%) I: 640 (49) C: 638 (48) HR 1,00, p = 0,93 4. <u>Mortality</u> Measured as all-cause mortality or death due to a cardiovascular event, n (%) *Total mortality, hazard ratio* I: 73 (6) C: 106 (8)	*Increased cardiovascular risk was defined by one or more of the following: clinical or subclinical cardiovascular disease other than stroke; chronic kidney disease, excluding polycystic kidney disease, with an estimated glomerular filtration rate (eGFR) of 20 to less than 60 ml per minute per 1.73 m2 of body surface area, calculated with the use of the four variable Modification of Diet in Renal Disease equation; a 10-year risk of cardiovascular disease of 15% or greater on the basis of the Framingham

		Groups comparable at baseline?				HR 0,68 (95%-CI 0,50-0,92), stratified according to clinic *Death due to cardiovascular event, hazard ratio* I: 11 (1) C: 11 (1) HR 0,97 (95%-CI 0,42-2,25), adjusted for sex, age, BMI, smoking, dyslipidaemia, diabetes mellitus, and antihypertensive agents used before enrolment. 5. <u>CVD</u> Measured as composite outcome: myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, or death from cardiovascular causes, n (%) I: 101 (8) C: 144 (11)	risk score; or an age of 75 years or older. **In both groups, injurious falls was among the most frequent serious adverse events. Among patients under intensive treatment also frequent was acute kidney injury or acute renal failure.

						HR 0,67 (0,51-0,86) 6. <u>Blood pressure</u> Not stated for the subgroup	

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders)**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders**

Study reference (first author, publication year)	**Describe method of randomisation[1]**	**Bias due to inadequate concealment of allocation?[2]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?[4]** (unlikely/likely/unclear)	**Bias due to loss to follow-up?[5]** (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?[6]** (unlikely/likely/unclear)
Antihypertensive versus placebo								
Beckett, 2008 (HYVET)	"Randomization was stratified according to age and sex; permuted blocks of 4 and 6 of any 10 patients were used to ensure roughly equal	Unclear. Not stated.	Unlikely. Matching placebo was given	Likely. Investigators were allowed to adjust the study medication according the blood pressure target.	Unlikely. "All events that were possible end points were reviewed by an independent committee, unaware of the group assignment, using predefined definitions from the protocol."	Unclear. Trial was registered retrospectively; although outcomes stated were reported.	Likely. Reasons for lost to follow-up were similar; however, total number was large and almost 50% in each group.	Unlikely. "The primary analysis was performed according to the intention-to-treat principle."

	assignment to each of the two groups within large centers."							
Steassen, 1998	"Eligible patients were prospectively stratified by center, sex, and previous cardiovascular complications and thereafter randomized to double-blind treatment with active medication or placebo by means of a computerized random function."	Unclear. Not stated.	Unlikely. Matching placebo was given.	Unclear. Not stated.	Unlikely. The End Point Committee, which was unaware of the patients' treatment, (…)."	Unclear. Not stated whether the trial was registered.	Unclear. More participants withdrew from double-blind treatment in the control group; however, reasons are not stated.	Unlikely. "The analysis by intention to treat included all end points occurring during double-blind and open follow-up, regardless of whether the patients were taking the treatment to which they had been randomized."
Intensive versus standard blood pressure control								
The SPRINT research group, 2015	"Randomization was stratified according to clinical site."	Unclear. Not stated.	Likely. "Participants and study personnel were aware of the study-group assignments, (…)."	Likely. "Participants and study personnel were aware of the study-group assignments, (…)."	Unlikely. "Participants and study personnel were aware of the study-group assignments, but	Unlikely. Trial registered prospectively with reported outcome stated in publication	Unclear. Not stated for the subgroup.	Unlikely. "(…) with the use of the intention-to-treat approach for all randomly assigned participants; (…)"

					outcome adjudicators were not."			
Wei, 2013	"(…) were randomly assigned to either intensive antihypertensive treatment or standard treatment by using a computer-generated table of random numbers."	Unclear. Not stated	Likely. Participants were not blinded	Likely. Care providers could not be blinded.	Unlikely. "(…), endpoints were evaluated by the members of the Endpoint Evaluation Committee, who were blinded to the treatment assignments and the time course of BP."	Unclear. It was not reported whether the trial was registered.	Unlikely. Although reasons for lost to follow-up were not clear, numbers were very small (<3%).	Unlikely. "An intention-to-treat analysis was performed to ensure that all study participants were followed until the conclusion of the study, irrespective of whether the participant was still receiving or complying with the treatment."
Ogihara, 2010	"(…), the patients were randomly assigned by the VALISH data center according to the following factors: sex, age (<75 or ≥75 years), systolic BP (<175 or ≥175 mmHg), antihypertensive therapy,	Unclear. Not stated	Likely. Participants were not blinded	Likely. Care providers could not be blinded.	Unlikely. "End points and adverse events were blindly evaluated according to the prospective, randomized, open-label, blinded end point design by the endpoint committee and the safety committee, respectively."	Unclear. It was not reported whether the trial was registered.	Unclear. Reasons for withdrawal were not stated.	Unlikely. "All of the registered study patients assigned to treatment were analysed on an intention-to-treat basis."

	and institution (weighting coefficient: 2).							

1. **Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.**
2. **Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..**
3. **Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.**
5. **If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the Risk of Bias is unclear**
6. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the Risk of Bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

Noot 35: Type antihypertensivum bij (kwetsbare) ouderen (> 70 jaar)

Evidencetabellen

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison/ control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Saruta, 2015 Additional data from Ogihara, 2014	Type of study: RCT (parallel) Setting: Patients with or without a history of cardiovascular disease	Inclusion criteria: - Aged 65-84 years - History of cardiovascular disease and/or cardiovascular risk factors - Systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg while on	Olmesartan plus a CCB (amlodipine or azelnidipine) for at least 3 years Target BP was <140/90 mmHg	Olmesartan plus a low-dose diuretic (trichlormethiazide, indapamide or some other thiazide) for at least 3 years Target BP was < 140/90 mmHg	Length of follow-up: Mean 3.3 years Loss-to-follow-up: Intervention: N = 46 (2%) Reasons: not clear Control: N = 72 (3%)	1. Events (CVD) Measured as a composite of fatal and non-fatal cardiovascular events, n (%) I: 116 (5) C: 135 (5) HR 0.83 (0,65 tot 1,07)	Authors' conclusions: "Total discontinuation rate, incidences of AEs, SAEs, drug-related SAEs and discontinuation due to SAEs were lower in the olmesartan plus CCB group than in the

	Country: Japan Source of funding: Non-commercial	antihypertensive treatment - Systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 100 mmHg without treatment <u>N total at baseline</u>: Intervention: 2568 Control: 2573 <u>Important prognostic factors</u>[2]: Age ± SD: I: 73 (5) C: 73 (5) Sex: I: 52% M C: 52% M History of CVD: I: 26% C: 26% Groups comparable at baseline? Yes			Reasons: not clear <u>Incomplete outcome data</u>: Intervention: N = 46 (2%) Reasons: not clear Control: N = 72 (3%) Reasons: not clear	2. <u>Quality of life</u> No data reported 3. <u>Functional status</u> No data reported 4. <u>Adverse events</u> Indicated as drug-related serious adverse events, n (%) *Gastrointestinal disorder* I: 1 (0,04) C: 1 (0,04) *Arrhythmia* I: 2 (0,1) C: 2 (0,1) *Renal dysfunction* I: 2 (0,1) C: 6 (0,2) *Miscellaneous* I: 5 (0,2) C: 16 (0,6) p = 0,02 5. <u>Mortality</u> Measured as all-cause mortality, n (%) I: 64 (3)	olmesartan plus diuretic group.

						C: 76 (3) HR 0.83 (95%-CI: 0,59-1,15) 6. Blood pressure Measured as the mean change from baseline, mean (SD) systolic/diastolic I: 24,4 (16,4)/ 13,8 (12,0) C: 24,9 (17,3)/ 13,7 (12,4) P > 0,05	
Wing, 2003	Type of study: RCT (parallel) Setting: Family medical practices Country: Australia Source of funding: Industry	Inclusion criteria: - Aged 65 to 84 years - An average systolic blood pressure, measured at the two study entry visits while the subject was sitting, of at least 160 mmHg or an average diastolic blood pressure of at least 90 mmHg (if the systolic blood pressure was at least 140 mmHg); - The absence of recent cardiovascular events (within	ACE-inhibitors	Diuretic	Length of follow-up: Median 4,1 years Loss-to-follow-up: Intervention: N = 66 (2%) Reasons: unclear Control: N = 102 (3%) Reasons: unclear Incomplete outcome data: Intervention: N = 66 (2%) Reasons: unclear Control: N = 102 (3%)	1. Events (CVD) Measured as a composite of fatal and non-fatal cardiovascular events, n (%) I: 394 (13) C: 429 (14) HR 0,89 (95%-CI: 0,79-1.00) 2. Quality of life No data reported 3. Functional status No data reported 4. Adverse events No data reported	

		the previous six months); - Willingness to give informed consent. <u>Exclusion criteria</u>: - Any life-threatening illness - Contraindication to an ACE inhibitor or diuretic - A plasma creatinine concentration of more than 2.5 mg per deciliter (221 µmol per liter) - Malignant hypertension - Dementia. <u>N total at baseline</u>: Intervention: 3044 Control: 3039 <u>Important prognostic factors</u>[2]: For example age ± SD: I: 72 C: 71			Reasons: unclear	5. <u>Mortality</u> Measured as all-cause mortality, n (%) I: 195 (6) C: 210 (7) HR 0.90 (95%-CI: 0.75-1.09) 6. <u>Blood pressure</u> Measured as the mean change from baseline, mean (SD) systolic/diastolic *Year 1* I: 20/9 mmHg C: 22/9 mmHg *Year 2* I: 23/10 mmHg C: 24/10 mmHg *Year 5* I: 26/12 mmHg C: 26/12 mmHg	

		Sex: I: 50% M C: 48% M Coronary heart disease: I: 8% C: 8% Groups comparable at baseline? Yes					
Cowley, 2000	Type of study: RCT (parallel) Setting: Heart failure patients Country: United States, Europe and South America* Source of funding: Industry**	Inclusion criteria: - Aged 65 years or more - ACE inhibitors naive - Symptomatic heart failure N total at baseline: Intervention: 147 Control: 153 Important prognostic factors[2]: Age ± SD: I: 73 (6) C: 73 (7) Sex: I: 73% M C: 80% M	Losartan (12.5 mg once daily, titrated to 50 mg once daily)	Captopril (6.25 mg three times daily, titrated to 50 mg thre times daily)	Length of follow-up: 48 weken Loss to follow-up: Intervention: N = 30 (20%) Reasons: 10 clinical adverse events, 5 deaths, 1 laboratory adverse event, 14 lost to follow-up/withdrew/protocol deviation Control: N = 45 (29%) Reasons: 21 clinical adverse events, 7 deaths, 1 laboratory adverse event, 1, therapy ineffective, 15 lost to follow-	1. Events (CVD) Data not reported 2. Quality of life Measured with heart failure disease-specific HRQoL (LIhFE) and more general HRQoL parameters (SIP) Numbers were displayed in figures. There was no difference in scores for both measure between groups. 3. Functional status No data reported 4. Adverse events No data reported	* Only data from US sites was decribed ** Part of the authors were employees and other authors were paid consultants.

		Groups comparable at baseline? Yes			up/withdrew/protocol deviation <u>Incomplete outcome data</u>: Intervention: N = 30 (20%) Reasons: 10 clinical adverse events, 5 deaths, 1 laboratory adverse event, 14 lost to follow-up/withdrew/protocol deviation Control: N = 45 (29%) Reasons: 21 clinical adverse events, 7 deaths, 1 laboratory adverse event, 1, therapy ineffective, 15 lost to follow-up/withdrew/protocol deviation	5. <u>Mortality</u> Data not reported 6. <u>Blood pressure</u> Data not reported	
Benetos, 2000	Type of study: RCT (parallel) Setting: General practitioners Country: France	<u>Inclusion criteria</u>: - Aged older than 60 years - Uncomplicated isolated systolic hypertension <u>Exclusion criteria</u>: - Malignant of secondary hypertension	Bisoprolol 2.5 mg/hydrochlorothiazide 6.25 mg combination, once daily, for 12 weeks	Amlodipine 5 mg, once daily, for 12 weeks	<u>Length of follow-up</u>: 12 weeks <u>Loss to follow-up</u>: Intervention: N = 11 (13%) Reasons: adverse events Control: N = 7 (9%)	1. <u>Events (CVD)</u> No data reported 2. <u>Quality of life</u> Assessed with a self-administered tool with 22 questions (score ranging from 22 5to 88) with a higher score	

	Source of funding: Commercial	- Heart failure, stroke of myocardial infarction within 3 months before enrolment - Obstructive myocardiopathy - Aortic aneurysm - Atrioventricular block of more than the first degree - Sinoauricular block - Bradycardia at rest < 50 beats/min - Intermittent claudication - Unstable angina - Severe renal or hepatic impairment - Asthma - Unstable diabetes mellitus - History of alcohol or drug abuse <u>N total at baseline</u>: Intervention: 83 Control: 77			Reasons: adverse events <u>Incomplete outcome data</u>: Intervention: N = 11 (13%) Reasons: adverse events Control: N = 7 (9%) Reasons: adverse events	indicating a greater sense of well-being. Numbers were displayed in figures. There was no difference in scores for both measure between groups. 3. <u>Functional status</u> No data reported 4. <u>Adverse events</u> Measured as any adverse event I: 48 (58%) C: 65 (84%) RR 0,69 (95%-CI: 0,56-0,84) 5. <u>Mortality</u> No data reported 6. <u>Blood pressure</u> Measured as the mean change from baseline, mean (SD) systolic/diastolic I: -20,0 (13,7)/ -4,5 (7,4) C: -19,6 (14,2)/ -2,4 (8,4) p = 0,85/ p = 0,09	

		Important prognostic factors[2]: Age ± SD: I: 72 (7) C: 73 (7) Sex: I: 29% M C: 47% M Groups comparable at baseline? Yes				24-h I: -12,2 (12,3)/ -8,4 (6,5) C: -8,1 (13,0)/ -3,6 (7,4) p = 0.16/ p = 0.004	

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders)**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders**

Study reference (first author, publication year)	**Describe method of randomisation[1]**	**Bias due to inadequate concealment of allocation?[2]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?[4]** (unlikely/likely/unclear)	**Bias due to loss to follow-up?[5]** (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?[6]** (unlikely/likely/unclear)
Saruta, 2015 and Ogihara, 2014	"Patients were randomized 1:1 using a dynamic	Unclear. Not clearly stated.	Unclear. Unknown whether prescribed medications were identical in appearance.	Likely. Investigator made to choose which CCB and diuretic was prescribed.	Unclear. Not stated	Unlikely. Rational, design was published before study.	Unlikely. Less than 5% in each arm was lost to follow-up	Unlikely. "All analyses were conducted according to the

	allocation method with stratification for sex, age, history of cardiovascular disease, BP, prior use of antihypertensive agents, and centre. Randomization was conducted using a computerized system by the COLM study data centre, and the random allocation sequence was concealed until the end of the enrolment period. “							intention-to-treat principle.”
Wing, 2003	“Subjects were randomly assigned centrally by telephone to	Unlikely.	Unclear. Unknown whether prescribed medications were identical in appearance.	Unclear. Not stated	Unlikely. “An end-point committee whose members were unaware of the treatment-group assignments	Unclear. Study was not registered. However, all outcomes in the methods section	Unlikely. Less than 5% was lost to follow in each group.	Unlikely. “All results are based on intention-to-treat analyses.”

	either ACE-inhibitor-based or diuretic-based treatment."				adjudicated all potential end points."	were reported in the results.		
Cowley, 2000	"(…) were randomised in blinded fashion to (…).	Unclear. Not stated	Unlikely. "Double-blinding was maintained as all patients received placebo-matching controls (…)."	Unclear. Not stated.	Unclear. Not stated.	Unclear. Trial was not registered. However, all outcomes in the methods section were reported in the results.	Likely. More than 20% in each group was lost to follow-up with more clinical adverse events in one group.	Unclear. Not stated
Benetos, 2000	"Those who qualified were randomly assigned to receive (…)."	Unclear. Not stated.	Unclear. Unknown whether prescribed medications were identical in appearance.	Unclear. Not stated.	Unclear. Not stated.	Unclear. Trial was not registered. However, all outcomes in the methods section were reported in the results.	Unlikely. Percentage of lost-follow-up was similar in each group.	Unlikely. "Statistical analyses were performed for the intent-to-treat population (…)"

1. **Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.**
2. **Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..**
3. **Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.**
5. **If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the Risk of Bias is unclear**
6. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the Risk of Bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

Noot 36: Stoppen met antihypertensiva bij (kwetsbare) ouderen (> 70 jaar)

Evidencetabellen

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison/ control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Moonen, 2015	Type of study: RCT Setting: community based, 128 general practices in and around Leiden. Country: The Netherlands Source of funding: Not industry sponsored	Inclusion criteria: • 75 years or older • Used antihypertensive treatment • Systolic blood pressure ≤160 mmHg • Mini-Mental State Examination (MMSE) score of 21 to 27. Exclusion criteria: • Clinical diagnosis of dementia • Use of antihypertensives for reasons other than hypertension • Current angina pectoris, cardiac arrhythmia, heart failure, myocardial infarction or a coronary reperfusion procedure less than 3 years ago • History of stroke or transient ischemic attack	Describe intervention (treatment/procedure/test): Discontinuation of antihypertensive treatment: Antihypertensive treatment was discontinued during a 6-week period after randomisation according to an algorithm, and until systolic blood pressure reached a maximal increase of 20 mmHg. Withdrawal of medication was done by the participant's physician, he/she monitored blood pressure every week until no further changes in treatment were made. Antihypertensive medication had to be restarted in week 6-16 after randomisation if • Diastolic BP ≥ 120 mmHG • Systolic BP ≥ 200 mmHG (180 for patients with diabetes mellitus or with cardiovascular event >3 years ago)	Describe control (treatment/procedure/test): Continuation of antihypertensive treatment	Length of follow-up: 16 weeks Loss to follow-up: Intervention: 19 (9,5%) Reasons: 1 died, 11 withdrew consent, 7 health reasons Control: 10 (5.4%) Reasons: 1 died, 5 withdrew consent, 4 health reasons. Incomplete outcome data: See above, data incomplete only due to	1. Quality of life (Cantril Ladder, range 1-10, higher scores indicate better quality of life) Difference = -0,09, 95%-CI=-0,34;0,16. 2. CVD events I: 1 stroke, 1 myocardial infarction and 1 transient ischemic attack C: 1 myocardial infarction and 1 transient ischemic attack Given this small number of events, it is not possible to determine the effect of the	45 (23%) of the patients in the intervention group did not receive the intervention as randomized. Frequent reasons included: BP that exceeded safety limits (n = 24), atrial fibrillation (n = 3), not showing up for intervention (n = 4), unknown (n = 9). After randomisation 8 participants were excluded, as they did not meet eligibility criteria.

		• Limited life expectancy In case patients had a history of peripheral arterial disease, myocardial infarction, coronoary reperfysion procedure or when diagnosed with diabetes, participation was possible when the systolic blood pressure ≤ 140 mmHg <u>N total at baseline</u>: Intervention: 199 Control:186 <u>Important prognostic factors:</u>[2] Reported for the participants that completed the study (n = 356) *age ± SD:* *I: 81,1 (4,3)* *C:81,5 (4,6)* *Sex:* *I: 42.8% M*	• Increase in systolic BP of ≥60 mmHG as compared to baseline.		loss-to-follow-up.	intervention on CVD events. <u>3. Mortality (all-cause and CVD)</u> I: 1 C: 1 Given this small number of causes, it is not possible to determine the effect of the intervention on mortality. <u>4. function</u> Cognitive function (Overall compound cognitive score, (mean of standardized z-scores across 6 tests: MMSE, The Trail Making Test parts A and B, the Interference score of the abbreviated	

		C: 39.8% M *Global cognitive functioning, MMSE, median (IQR):* *I: 26 (25-27)* *C: 26 (25-27)* Groups comparable at baseline? Participants in de intervention group used slightly less often B- Blockers and had slightly worse scores on the Trail Making Test difference score.				Stroop Color-Word Test, 15 Word Verbal Learning Test, Visual Association Test and the Letter digit Substitution Test) Difference = 0,02, 95%-CI = -0,19;0,23. General daily functioning (Groningen Activity Restriction scale, range 18 to 72 points, higher scores indicate lower functioning). Difference = -0,72, 95%-CI = -1,52;0,09. <u>5. Blood pressure</u> Systolic blood pressure at 16 week: SBP was higher in the	

						intervention group. Difference = 7,36, 95%-CI = 3,02;11,69 Diastolic blood pressure at 16 weeks: DBP was higher in the intervention group. Difference = 2,63, 95%-CI= 0,34;4,93. <u>6. disease free survival</u> Not reported	

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders)**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders**

Study reference (first author, publication year)	**Describe method of randomisation[1]**	**Bias due to inadequate concealment of allocation?[2]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?[3]** (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?[4]** (unlikely/likely/unclear)	**Bias due to loss to follow-up?[5]** (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?[6]** (unlikely/likely/unclear)
Moonen, 2015	"Concealment of treatment allocation was ensured by a central computerized randomization procedure. Participants were randomly assigned, in a 1:1 ratio, to parallel discontinuation (intervention group) or continuation (control group) of antihypertensive treatment".	Unlikely	Likely	Likely	Unlikely	Unlikely	Unclear	Unlikely

	"Stratified block randomization was used (with block sizes of 4 per general practice) …."							

1. **Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.**
2. **Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules.**
3. **Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.**
5. **If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the Risk of Bias is unclear**
6. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the Risk of Bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

Noot 38: Starten met trombocytenaggregatieremmers bij (kwetsbare) ouderen (> 70 jaar)

Evidencetabellen

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison/ control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Primary prevention							
Silagy, 1993	Type of study: RCT Setting: Community (including general practice, residential retirement villages, and from the electoral roll) Country: Australia Source of funding: Industry sponsored	Inclusion criteria: • 70 years or older Exclusion criteria: • Clinical history of major pre-existing cardiovascular disease • Existing contraindication to the use of aspirin • Receiving concomitant treatment with nonsteroidal anti-inflammatory drugs N total at baseline: Intervention: 200 Control: 200 Important prognostic factors[2]:	100 mg aspirin daily	Matching placebo daily	Length of follow-up: 12 months Loss-to-follow-up: N = 0 (0%) Incomplete outcome data: N = 58 (15%) Reasons: Of 58, 16% due to commencement of non-steroidal drugs; 9% developed side effects; and 75% unable or unwilling to continue with the demands of the study	1.Quality of life Not reported 2.Cognitive function Not reported 3.Adverse events (bleeding) Defined as any bleeding symptoms I: 34 (17%) C: 19 (10%) RR 1,79 (95%-CI: 1,06-3,03) Defined as gastrointestinal bleeding I: 6 (3%) C: 0 (0%) RR cannot be calculated 4.Mortality (all-cause and CVD) "No distinction (between event rates for both fatal and non-fatal cardiovascular disease)	

		Age groups: Intervention 70 to 74: 52% 75 to 79: 33% 80 to 84: 14% 85+: 2% Control 70 to 74: 57% 75 to 79: 31% 80 to 84: 9% 85+: 4% Sex: I: 49% M C: 50% M Current smoker: I: 5% C: 7% Groups comparable at baseline? Yes				was made between the treatment and control group since there were insufficient events." 5.<u>CVD events</u> Only angina was reported separately by treatment group *Angina* I: 1 (1%) C: 3 (2%) RR 0,33 (95%-BI 0,03 to 3,18) "No distinction (between event rates for both fatal and non-fatal cardiovascular disease) was made between the treatment and control group since there were insufficient events." 6.<u>Disease-free survival</u> Not reported	
Secondary prevention							
Sivenius, 1999	Type of study: RCT Setting: Patients with	<u>Inclusion criteria</u>: • Recent (less than 3 months) TIA or stroke	25 mg acetylsalicylic acid, twice daily	Placebo	<u>Length of follow-up</u>: 2 years <u>Loss to follow-up</u>: N = 0 (0%)	1.<u>Quality of life</u> Not reported 2.<u>Cognitive function</u> Not reported	Only subgroup among 75 years or older taken into account.

	a recent TIA or stroke (less than 3 months) Country: 13 countries Source of funding: Not stated	N total at baseline: Intervention: 1649 (aged 75 or older: 468) Control: 1649 (aged 75 or older: 427) Important prognostic factors:[2] Not reported			Incomplete outcome data: Unknown	3.Adverse events (bleeding) Not reported 4.Mortality (all-cause and CVD) Cannot be interpreted; definite as a composite endpoint stroke and/or death 5.CVD events Composite endpoints, defined as vascular death, non-fatal stroke, non-fatal myocardial infarction or non-fatal other vascular event. I: 132/468 (28%) C: 134/427 (31%) RR 0,90 (95%-BI 0,73-1,10) 6.Disease-free survival Not reported	

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures**
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Study reference (first author, publication year)	Describe method of randomisation[1]	Bias due to inadequate concealment of allocation?[2] (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?[4] (unlikely/likely/unclear)	Bias due to loss to follow-up?[5] (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?[6] (unlikely/likely/unclear)
Primary prevention								
Silagy, 1993	"Subjects were allocated randomly in a 1:1 ratio to receive either 100 mg of aspirin or matching placebo daily."	Unclear; not stated	Unlikely; a matching placebo was used	Unclear; not stated	Unclear; not stated	Unclear; not mentioned whether trial was registered	Unclear; not mentioned how many in each arm drop-out	Unclear; not stated
Secondary prevention								
Sivenius, 1999	"ESPS2 was a randomized, 2 x 2 factorial, double-blind, placebo-controlled, multicentre trial (…)."	Unclear; not stated	Unclear; stated to be a double-blind study, but not who was blinded	Unclear; stated to be a double-blind study, but not who was blinded	Unclear; stated to be a double-blind study, but not who was blinded	Unclear; not mentioned whether trial was registered	Unlikely; none were lost to follow-up	Unclear; not stated

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2. **Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules.**
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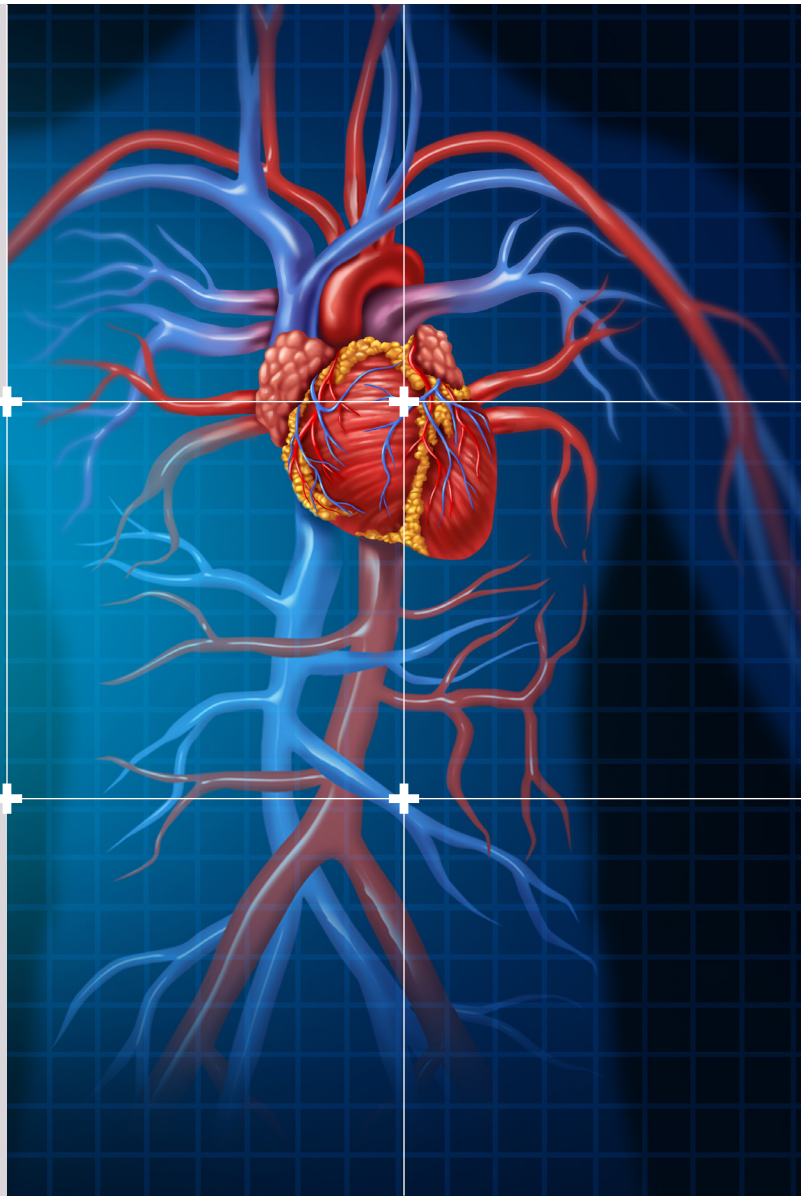
6. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the Risk of Bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

Totstandkoming en methoden
NHG-Standaard CVRM (M84)

Mei 2019



Mercatorlaan 1200
3528 BL Utrecht
Postbus 3231
3502 GE Utrecht

088 - 506 55 00
info@nhg.org
www.nhg.org

Nederlands
Huisartsen
Genootschap