KCE REPORT 244S

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

NON-INVASIVE MARKERS OF SUBCLINICAL ATHEROSCLEROSIS FOR PREDICTING A PRIMARY CARDIOVASCULAR EVENT: A RAPID SYSTEMATIC REVIEW

APPENDIX

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HEALTH TECHNOLOGY ASSESSMENT

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APPENDIX

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COLOPHON

Title:	Non-invasive markers of subclinical atherosclerosis for predicting a primary cardiovascular event: a rapid systematic review – Appendix
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APPENDIX REPORT

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1. SEARCH STRATEGY – CLINICAL REVIEW

1.1. Medline @ PUBMED

Date	19-09-2014		16-12-2014		12-01-2015	
Database	Medline (PUBMED)					
Search Strategy	**#**	***Query***	***Results***	***Query***	***Results***	***Query***	***Results***
	1	cardiovascular diseases [MH]	1872624	cardiovascular diseases [MH]	1889538		
	2	Cardiovascular [TIAB]	284667	Cardiovascular [TIAB]	289711		
	3	Stroke [TIAB]	149507	Stroke [TIAB]	152486		
	4	Cerebrovascular [TIAB]	38508	Cerebrovascular [TIAB]	38996		
	5	Coronary [TIAB]	370714	Coronary [TIAB]	308979		
	6	Myocardial infarction [TIAB]	134410	Myocardial infarction [TIAB]	135689		
	7	1 OR 2 OR 3 OR 4 OR 5 OR 6	624939	1 OR 2 OR 3 OR 4 OR 5 OR 6	2144300	Carotid Plaque* OR "Plaque, Atherosclerotic"[Mesh]	**5466**
	8	Carotid intima-media thickness [MH]	1415	Pulse wave velocity [TIAB]	4998	Pulse wave velocity [TIAB]	**5075**
	9	“Carotid intima-media thickness”	7659	Arterial stiffness [TIAB]	4855	Arterial stiffness [TIAB]4	**4938**
	10	Ankle-brachial index [MH]	1367	Plaque* OR "Plaque, Atherosclerotic"[Mesh]	109625	Ankle-brachial index [MH]	**1486**
	11	“Ankle-brachial index”	3492	8 OR 9 OR 10	116796	“Ankle-brachial index”	**3637**
	12	Liver attenuation [TIAB]	97				
	13	“pericardial adipose tissue”	47				
	14	calcium or calcinosis or calcification	538458				
	15	“inter-arm blood pressure difference” or “brachial-brachial index”	13			“inter-arm blood pressure difference” or “brachial-brachial index”	**14**
	16	"brachial flow-mediated dilation"	94				
	17	8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15	548803			7 OR 8 OR 9 OR 10 OR 11 OR 15	**16055**

	18	Reclassification OR reclassified OR NRI	6550	Reclassification OR reclassified OR NRI	6714	Framingham OR SCORE OR conventional OR traditional	**860 855**
	19	7 AND 17 AND 18	172	7 AND 11 AND 18	79	Primary OR 'general population' OR asymptomatic	**1290994**
	20	19 AND publication date from 2008/01/01 to 2014/12/31	159	19 AND publication date from 2008/01/01 to 2014/12/31	76	17 AND 18 AND 19	**492**
						Limit: randomized controlled trial	**30**
						screening	

Note

1.2. EMBASE

Date	**19-09-2014**		**26/12/2014**		**12/01/2015**	
Database	EMBASE					
Search Strategy	**#**	***Query***	***Results***	***Query***	***Results***	***Query***	***Results***
	1	'cardiovascular disease'/exp	3067242	'cardiovascular disease'/exp	3,137,392		
	2	Cardiovascular:ab,ti	384725	Cardiovascular:ab,ti	394,722		
	3	Stroke:ab,ti	211231	Stroke:ab,ti	267,761		
	4	Cerebrovascular:ab,ti	51249	Cerebrovascular:ab,ti	52,568		
	5	Coronary:ab,ti	397948	Coronary:ab,ti	406,810		
	6	'Myocardial infarction':ab,ti	181196	'Myocardial infarction':ab,ti	185,697		
	7	1 OR 2 OR 3 OR 4 OR 5 OR 6	3263069	1 OR 2 OR 3 OR 4 OR 5 OR 6	3,318,194		
	8	'Carotid intima-media thickness'	5889	'Pulse wave velocity':ab,ti	8,503	'Pulse wave velocity':ab,ti	**8 635**

	9	'Ankle-brachial index'/exp	5399	'Arterial stiffness':ab,ti	8,184	'Arterial stiffness':ab,ti	**8 320**
	10	'Ankle-brachial index':ab,ti	4096	Plaque*:ab,ti OR 'atherosclerotic plaque'/exp	127,270	Carotid plaque*:ab,ti OR 'atherosclerotic plaque'/exp	**30 114**
	11	'Liver attenuation'	167	8 OR 9 OR 10	139,027	'Ankle-brachial index'/exp	**5705**
	12	'pericardial adipose tissue'	104			'inter-arm blood pressure difference' OR 'brachial-brachial index'	**27**
	13	calcium OR calcinosis OR calcification	695511			coronary AND (calcium OR calcinosis OR calcification)	**37448**
	14	'inter-arm blood pressure difference' OR 'brachial-brachial index'	26			8 OR 9 OR 10 OR 11 OR 12 OR 13	**81 457**
	15	'brachial flow-mediated dilation'	134			Framingham OR SCORE OR conventional OR traditional	**1 158 385**
	16	8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15	12476			Primary OR 'general population' OR asymptomatic	**1 661 437**
	17	Reclassification OR reclassified OR NRI	9118	Reclassification OR reclassified OR NRI	9,496	14 AND 15 AND 16	**2 817**
	18	7 AND 16 AND 17	114	7AND 11 AND 17	161	Limit: randomized controlled trial	**126**
	19	18 AND publication date from 2008/01/01 to 2014/12/31	111	18 AND publication date from 2008/01/01 to 2014/12/31	157		
Note							

1.3. Cochrane Database of Systematic Reviews

Date	**19-09-2014**		
Database	**Cochrane Library of Systematic Reviews**		
Search Strategy	**#**	***Query***	***Results***
	1	MeSH descriptor: [cardiovascular disease] explode all trees	**75493**
	2	Cardiovascular: ab,ti	**26628**
	3	Stroke: ab,ti	**20981**
	4	Cerebrovascular: ab, ti	**2228**
	5	Coronary: ab,ti	**26036**
	6	'Myocardial infarction':ab,ti	**13829**
	7	1 OR 2 OR 3 OR 4 OR 5 OR 6	**114338**
	8	'Carotid intima-media thickness'	**443**
	9	'Ankle-brachial index'/exp	**113**
	10	'Ankle-brachial index':ab,ti	**413**
	11	'Liver attenuation'	**7**
	12	'pericardial adipose tissue'	**1**
	13	calcium OR calcinosis OR calcification	**17709**
	14	'inter-arm blood pressure difference' OR 'brachial-brachial index'	**0**
	15	'brachial flow-mediated dilation'	**12**
	16	8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15	**18501**
	17	Reclassification OR reclassified OR NRI	**182**
	18	7 AND 16 AND 17	**7**
	19	19 AND publication date from 2008/01/01 to 2014/12/31	**7**
Note			

1.4. DARE and HTA database (CRD)

Date	**19-09-2014**		
Database	**CRD**		
Search Strategy	**#**	***Query***	*Results*
	1	cardiovascular	
	2	Reclassification	
	3	reclassified	
	4	NRI	
	5	#2 OR #3 OR #4	
	6	#1 AND #5	
	19	19 AND publication date from 2008/01/01 to 2014/12/31	**7**
Note			

2. QUALITY APPRAISAL – CLINICAL EVIDENCE

2.1. Peters 2012

Peters 2012 [1]	
1. Methods	
Design	Systematic review
Source of funding and competing interest	The review was conducted by the Kaiser Permanente Research Affiliates Evidence-based Practice Center under contract to AHRQ
Search date	7 September 2011
Searched databases	MEDLINE
Included study designs	Studies assessing the added value of non-invasive imaging markers of subclinical atherosclerosis on top of traditional risk algorithms in risk prediction for CVD in individuals without symptomatic CVD or diabetes mellitus.
Number of included studies	Of the final 25 studies, two studies used FMD as a marker to improve risk prediction, 12 studies used CIMT, six studies used carotid plaques and nine studies used CAC
Statistical analysis	Limited number, heterogeneity, and nature of included studies did not allow for quantitative synthesis
2. Patient characteristics	
Eligibility criteria	Publications were selected that specifically studied the incremental prognostic value of non-invasive measurable markers of atherosclerosis when added to a risk model consisting of traditional risk factors rather than evaluating the predictive value of these markers in isolation.
Exclusion criteria	NR
Patient & disease characteristics	Individuals without symptomatic CVD or diabetes mellitus
3. Interventions	
Intervention group	CVD prediction based on FRS + atherosclerosis markers
Control group	CVD prediction based on FRS only
4. Results	
Outcome: NRI	See report for NRI and CNRI for each atherosclerosis marker
5. Limitations and other comments	
Limitations	• Only Medline was searched. However, the review was carried out by people well aware of the domain, which probably limited the risk that important studies were missed.

2.1.1. Amstar: Peters 2012[1]

Item	Score	Justification
1. Was an 'a priori' design provided?	Can't answer	Not reported
2. Was there duplicate study selection and data extraction?	Yes	Publications were reviewed in duplicate (by SAEP and HMR) and the references of the selected studies were examined.
3. Was a comprehensive literature search performed?	No	Only Medline (Pubmed) was searched, and language was restricted to English
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No	
5. Was a list of studies (included and excluded) provided?	Yes	Reasons for exclusion were provided but individual studies were not listed
6. Were the characteristics of the included studies provided?	Yes	
7. Was the scientific quality of the included studies assessed and documented?	Yes	Partially only. The parameters in the supplemental table are unclear, and the table focuses essentially on the reporting
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	
9. Were the methods used to combine the findings of studies appropriate?	Not applicable	

2.2. Lin 2013

Lin 2013[2]	
1. Methods	
Design	Systematic review
Source of funding and competing interest	The review was conducted by the Kaiser Permanente Research Affiliates Evidence-based Practice Center under contract to AHRQ
Search date	September 2012
Searched databases	MEDLINE, Cochrane Central Register of Controlled Trials; ClinicalTrials.gov (for ongoing trials)
Included study designs	Population-based prospective cohort risk prediction studies
Number of included studies	1 fair-quality meta-analysis (including data from 16 population-based cohorts) and 2 fair to good-quality primary studies (patients=52 510) 4 studies (n=22 055) reported on the NRI
Statistical analysis	Limited number, heterogeneity, and nature of included studies did not allow for quantitative synthesis
2. Patient characteristics	
Eligibility criteria	Studies that adjusted for, at a minimum, all of the FRS patient characteristics as defined by the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) (age, sex, smoking status, systolic blood pressure, total cholesterol level, and high-density lipoprotein cholesterol level)
Exclusion criteria	Studies not including (at a minimum) all of the ATP III's FRS factors in multivariate models
Patient & disease characteristics	Persons without known peripheral artery disease (PAD), coronary artery disease (CAD), cerebrovascular disease, diabetes, or severe chronic kidney disease
3. Interventions	
Intervention group	CVD prediction based on FRS + ABI
Control group	CVD prediction based on FRS only
4. Results	
Outcome: NRI	NRI was small when the ABI was added to the FRS to predict CAD or CVD events See table from paper below
5. Limitations and other comments	

Limitations	• Included studies defined risk categories differently (The ATP III's FRS defines risk categories as low (<10% ten-year risk for hard CAD events), intermediate (10% to 20% risk), or high (>20% risk) • Only English-language studies were included (the experts did not suggest other non–English-language studies though)

2.2.1. AMSTAR: LIN 2013 [2]

Item	Score	Justification
1. Was an 'a priori' design provided?	Can't answer	Not reported
2. Was there duplicate study selection and data extraction?	Yes	"Two investigators independently reviewed abstracts and full-text articles for inclusion using predetermined criteria. We resolved discrepancies by consulting a third investigator." "One investigator extracted data, and a second investigator checked the extraction."
3. Was a comprehensive literature search performed?	Yes	Although EMBASE was not searched "We searched MEDLINE and the Cochrane Central Register of Controlled Trials from 1996 through September 2012 to locate relevant English-language studies. We supplemented searches with suggestions from experts and reference lists from existing systematic reviews. We also searched ClinicalTrials.gov on 12 September 2012 for ongoing trials."
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	
5. Was a list of studies (included and excluded) provided?	Yes	See the full report on www.uspreventiveservicetaskforce.org
6. Were the characteristics of the included studies provided?	Yes	
7. Was the scientific quality of the included studies assessed and documented?	Yes	"Two investigators independently critically appraised all relevant studies using the USPSTF's design-specific criteria supplemented by the National Institute for Health and Clinical Excellence methodology checklists, the Newcastle-Ottawa Scale, and criteria from Hayden and colleagues. In general, a good-quality study met all prespecified criteria. A fair-quality study did not meet (or it was unclear whether it met) at least 1 criterion but also had no known important limitation that could invalidate its results. A poor-quality study had a single fatal flaw or several important limitations."
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	http://www.uspreventiveservicestaskforce.org/uspstf05/pad/padrs.htm

Item	Score	Justification
9. Were the methods used to combine the findings of studies appropriate?	Yes	"We qualitatively summarized the included evidence because the limited number, heterogeneity, and nature of our included studies did not allow for quantitative synthesis."
10. Was the likelihood of publication bias assessed?	Not applicable	Too few studies, no pooled point of reference
11. Was the conflict of interest included?	Yes	

2.3. Ben Shlomo 2014

	Study identification	Ben Shlomo 2014 [3]
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Probably yes (only 4 cohorts among the 17 eligible ones could not be accessed; 3 unpublished cohorts were included). *Individuals experiencing an event after 5 years were censored.* It is not clear why the authors used this dispendious analysis strategy instead of model fitting
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Loss to follow up of individual studies not reported "All except 4 studies had information on all adjustment variables, and all except 5 studies had event rates and follow-up times for all outcome measures."
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Not addressed, various methods across studies
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Not addressed
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes. *Missing covariates: Four studies had missing covariate data (2/17 studies had 2 covariates missing (one missing diabetes, one missing smoking, both missing blood pressure medication) and 2/17 had 1 covariate missing (HDL-cholesterol)) and could only partially adjust for covariates in the final model.*

1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes. *NRI confidence intervals: Uncertainty around the whole sample NRI, for both 5-year and 10-year overall reclassification, is demonstrated with 95% confidence intervals for the NRI estimates, calculated using the svy set of commands within Stata. Strata were defined as each study, and the within-study uncertainty calculated; variances were calculated separately for reclassification amongst events and non-events and then summed (since the two groups are independent by definition). This variance was then used to calculate the standard error of the NRI and thus the 95% confidence interval.*

2.3.1. AMSTAR BEN-SHLOMO 2014 [3]

Item	Score	Justification
1. Was an 'a priori' design provided?	Yes	*The protocol pre-specified analyses of the following potential effect modifiers*
2. Was there duplicate study selection and data extraction?	No	
3. Was a comprehensive literature search performed?	Yes	Medline and Embase
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	a systematic review and used data from both newly published and unpublished cohorts
5. Was a list of studies (included and excluded) provided?	No	The list of individual cohorts which could not been accessed is not reported
6. Were the characteristics of the included studies provided?	Yes	
7. Was the scientific quality of the included studies assessed and documented?	No	
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	
9. Were the methods used to combine the findings of studies appropriate?	Yes	See online appendix for the computation of the NRI
10. Was the likelihood of publication bias assessed?	Not applicable	
11. Was the conflict of interest included?	Yes	

2.4. Fowkes 2014

Fowkes 2014 [4]	
Methods	
• Design	Cohort study (individual data from 18 prospective cohort studies)
• Source of funding and competing interest	National Heart, Lung, and Blood Institute No competing interest declared
• Setting	18 prospective cohort studies mainly in Europe and USA
• Sample size	24,375 men; 20,377 women Only 7.4% of data in men and 2.9% in women were missing, predominantly for total and high-density lipoprotein cholesterol (compensated by imputation)
• Duration and follow-up	Variable across studies (min: 5 years; max: 19.6 years)
• Statistical analysis	Two models were fitted each for the primary outcome of major coronary events (myocardial infarction or death due to coronary heart disease) and the secondary outcome of cardiovascular mortality (death due to coronary heart disease or stroke) using Cox's proportional hazards model, as follows: model 1: Framingham risk score25 fitted as a continuous variable (FRS); model 2: as per model 1 with addition of ABI group (FRS+ABI). NRIs were calculated taking account of censored data. Confidence intervals and p-values were derived using methods for the standard NRI.
Patient characteristics	
• Eligibility criteria	
• Exclusion criteria	Subjects with non-valid ABI, with prevalent coronary heart disease as defined in each study at baseline, and without follow up for vital status were excluded. Subjects classified as 'non-white' using individual study classifications were excluded.
• Patient & disease characteristics	Median age: Sex: Current smoking: Antihypertensive drug treatment:
Prediction	
• New model	FRS + ABI (categorized into four groups: <0.90, 0.91–1.10, 1.11–1.40, >1.40)
• Comparator	FRS only
• Outcome predicted	Major coronary events (myocardial infarction or death due to coronary heart disease) Cardiovascular mortality (death due to coronary heart disease or stroke)
• Risk categories	Major coronary events: low (<10% ten-year risk), intermediate (10% to 20% risk), or high (>20% risk)

	Cardiovascular mortality: <2% ten-year risk , 2–4%, and >5%
Results	
• NRI no event	
• NRI event	
• NRI total	Major coronary events in men: NRI=4.3% (95% CI: 0.0; 7.6%, p=0.050) Major coronary events in women: NRI=9.6% (95% CI: 6.1; 16.4%, p<0.001) Cardiovascular mortality in men: NRI=5.7% (95% CI: 2.7; 7.9%, p<0.001) Cardiovascular mortality in women: NRI=15.7% (95% CI 11.3; 20.2%, p<0.001)
• NRI total in intermediate risk category	Major coronary events in men: NRI=15.9% (95% CI: 6.1; 20.6%, p<0.001) Major coronary events in women: NRI=23.3% (95% CI: 13.8; 62.5%, p<0.001) Cardiovascular mortality in men: NRI=20.2% (95% CI: 11.5; 29.1%, p<0.001) Cardiovascular mortality in women: NRI=18.0% (95% CI 13.1; 22.9%, p<0.001)
Limitations and other comments	
• Limitations	-Measurement of variables, including ABI, and the ascertainment and definition of endpoints were not identical across studies. However, studies were only included where consistent and valid methods were used. -Individuals with other CVD than coronary heart disease at baseline were not excluded. However, their number was reportedly low - Results in the external validation dataset were very different. This might be due to the fact that studies in the external validation dataset were the ones with one or more wholly imputed covariate, but also to the fact that the models were not calibrated for the baseline risk of these different populations? -The difference of NRI between men and women when ABI is added to FRS is doubtful and not supported by rational arguments

	Study identification	Fowkes 2014[4]
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes. *The study was based on 20 cohort datasets in the ABI Collaboration.*
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes. *Only 7.4% of data in men and 2.9% in women were missing, predominantly for total and high-density lipoprotein cholesterol. Imputation was performed separately by gender using the SAS procedure PROC MI with the MCMC full-data imputation method*.

1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes. *Framingham covariates extracted were age, gender, systolic and diastolic blood pressures, total and high density lipoprotein cholesterol, and smoking and diabetes indicators.*
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

2.5. Den Ruitjer 2012

Den Ruitjer 2012[5]	
Methods	
• **Design**	Cohort study USE-IMT (individual data from 14 prospective cohort studies)
• **Source of funding and competing interest**	The Netherlands Organisation for Health Research and Development In spite of the many disclosures of various funding by the authors, there was no obvious competing interest
• **Setting**	14 prospective cohort studies
• **Sample size**	45 828 individuals 2.2% missing data points, which were imputed using single imputation for each cohort separately (using the Multivariate Imputation by Chained Equations package of R)
• **Duration and follow-up**	Median: 10.8 (IQR: 6.9; 13.2)
• **Statistical analysis**	NRI taking survival time into account. The corresponding 95% confidence intervals were obtained with bootstrapping.
Patient characteristics	
• **Eligibility criteria**	aged 45-75 years, systolic blood pressure<180 mm Hg, total cholesterol<300 mg/dL, no symptomatic cardiovascular disease at baseline
• **Exclusion criteria**	

• **Patient & disease characteristics**	Median age: 58 (IQR: 35;75) Sex: 47.4% males Current smoking: 22% Antihypertensive drug treatment: 24%
Prediction	
• **New model**	FRS + cIMT
• **Comparator**	FRS only
• **Outcome predicted**	Myocardial infarction or stroke. First-time myocardial infarction and first time stroke were included as a combined end point. These included both fatal and nonfatal events.
• **Risk categories**	The 10-year absolute risk to develop a myocardial infarction or stroke was calculated and was used to classify individuals into risk categories of less than5%(low risk), 5% to less than 20% (intermediate risk), 20% or greater (high risk) according to the risk classification of the Framingham Heart Study
Results	
• **NRI no event**	0.5%
• **NRI event**	0.4%
• **NRI total**	0.8% (95%CI: 0.1; 1.6). No difference between males and females
• **NRI total in intermediate risk category**	3.6% (95%CI: 2.7; 4.6) No difference between males and females
Limitations and other comments	
• **Limitations**	• 16 of the eligible cohorts did not participate. The resulting potential bias is not discussed by the authors. The most important published cohorts were included, though. • Analysis was based on measurements of the mean common CIMT. Measurements of CIMT obtained from other carotid segments and the inclusion of a separate measure of carotid plaque may be important in risk prediction. Added value of CIMT measurements from other sites than the common carotid segment (eg, maximal CIMT) obtainable by carotid ultrasound is yet to be determined [6]. • Adjudication of events may have differed across studies but it is unlikely that this could have introduced a bias

	Study identification	Den Ruitjer 2012[5]
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	*Of the 63 514 individuals included in USE-IMT, we selected 45 828 individuals to whom the cardiovascular risk scores like Framingham Risk Score apply (aged 45-75 years, systolic blood pressure <180 mm Hg, total cholesterol <300 mg/dL; no symptomatic cardiovascular disease at baseline). Using these criteria, the number of excluded individuals was 6154 because of age, 2977 for total cholesterol level, 1757 for systolic pressure, and 7740 for previous cardiovascular disease (not mutually exclusive).*
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes. *Incomplete data on common CIMT, cardiovascular risk factors, and (time to) events resulted in 2.2% missing data points, which were imputed using single imputation for each cohort separately (using the Multivariate Imputation by Chained Equations package of R). Predictors in our imputation model included all variables in our database including the outcome of interest, as recommended previously. For a sensitivity analysis, we also performed a complete case analysis*
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

2.6. Yeboah 2012

	Study identification	Yeboah 2012[7]
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes. The full cohort includes 6814 women and men aged 45 to 84 years without known CVD, recruited from 6 US communities. The race/ethnic breakdown of MESA participants was 38% white, 28% black, 22% Hispanic, and 12% Chinese adults. However, The final study population included 1330 participants without diabetes mellitus, with an FRS of more than 5% to less than 20%, and with complete data on all 6 of the novel risk markers. The number of individuals excluded because of incomplete data on biomarkers is unknown.
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Loss to follow-up not reported
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	NA
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

2.7. Möhlenkamp 2011

	Study identification	Möhlenkamp 2011[8]
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	The Heinz Nixdorf Recall (HNR) study is a populationbased cohort study designed to assess the predictive value of novel markers of risk when used in addition to traditional risk. Participants were randomly selected from mandatory city registries in Essen, Bochum, and Mülheim, and invited to participate in the study as previously reported. Physician- or self-referral was not allowed to avoid selection bias. A total of 4,814 subjects aged 45 to 75 years (50% females) were included between December 2000 and August 2003.
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Of the remaining participants, 34 (0.8%) were lost to follow-up, in n 94 (2.1%), we were unable to obtain 5-year primary end point information, and in 244 (5.4%), 1 or more measurements of cardiovascular risk factors, hsCRP, or CAC were unavailable. Subjects with hsCRP. 10 mg/l suggesting acute inflammation were excluded (n=149, 3.3%), leaving 3,966 subjects (53% women) for this analysis.
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	NR
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

2.8. Kavousi 2012

	Study identification	Kavousi 2012[9]
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Unclear The study population is 6948 participants at the third examination of the original Rotterdam Study-I. What this number represents in term of the original cohort is not described. The CAC score was measured in 3678 individuals. *How this smaller group was selected is unclear. general characteristics of that subpopulation* *did not materially differ from those of the larger population.* *Our cohort comprised white participants aged 55 years or older; therefore, the generalizability of our findings to younger and nonwhite populations remains uncertain.*
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes Only 20 patients lost-to-follow up
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes? Not described in this paper
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes "We obtained information on study outcomes from general practitioners and from letters and discharge reports from medical specialists. Events were classified by study physicians. Incident CHD was defined as a definite nonfatal or fatal myocardial infarction or death due to CHD. Definite and possible fatal CHD were coded by using the definitions applied within the Cardiovascular Health Study and Atherosclerosis Risk in Communities Study. Only first CHD events were included in the analyses
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	NR
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes? • Because median follow-up in the cohort was 6.8 years and most CHD risk prediction instruments, including the FRS, predict 10-year CHD risk, we used a parametric Weibull proportional hazards regression model to estimate 10-year CHD risk from data available over a shorter follow-up period for each person.

	• Information on some markers and covariables was missing in up to 13% of participants. We performed multiple imputations of the missing values by using the Hmisc library of R

2.9. Pereira 2014

	Study identification	Pereira 2014 [10]
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Probably. *This study represents a re-analysis of the EDIVA project database, aiming to ascertain whether the inclusion of aortic PWV to the HeartSCORE adds discriminative capacity for MACE. The study population consisted of 2200 Portuguese nationals (1290 men and 910 women), aged between 18 and 91 years. For the present analysis, we selected from the original database, individuals aged above 35 years and without symptomatic cardiovascular disease, resulting in a cohort of 1709 individuals, 744 female and 944 males.*
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	NR
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes. *Carotid – femoral PWV was determined using a Complior ® device (Colson, Paris). Briefly, PWV was based on the distance/time ratio (m/s) with the pulse wave measured simultaneously in the right carotid and right femoral arteries, the distance used being that between the sites where the pressure waves were recorded. Measurements were performed by the same operator and the quality of the recordings was evaluated by two independent observers with considerable experience of the method. The reproducibility of these estimates previously determined in our laboratory showed correlation coeffi cients better than 0.9 (0.98 and 0.95, respectively, for inter- and intra-observer differences)*
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Not described

1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes. However, the tables for reclassification were not presented. In cases of small number of events, the NRI can be misleading. *To compare the discriminatory power of PWV in addition to the SCORE risk model, we estimated measures of model fi t, discrimination and calibration. Model fit was measured with the likelihood ratio test, the Akaike information criterion and the Schwartz ' s Bayesian information criterion; Harrell ' s C-index was used as a measure of discrimination. The Hosmer – Lemeshow test was used to check calibration of the models. In order to check the discrimination and reclassifi cation improvement, we computed the predicted risk for all of the participants using a Cox model that included only the standard risk factors. Using predicted risk from this model, we defined cut points for risk groups based on the predicted risk in participants who experienced an event within 2 years. We cross-classified categories of risk on the basis of a model that included standard risk factors against those based on a model that added PWV. The net reclassification improvement (NRI) and the integrated discrimination index improvement (IDI) were then derived.*

2.10. Pollak 2011

	Study identification	Pollak 2011[11]
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes. *The study population consisted of members of the Framingham Offspring Study cohort, composed of non-Hispanic whites, who were undergoing the sixth examination cycle, from February 1995 through September 1998. Of the 3532 persons seen during the clinic visit, 2965 who did not have current disease underwent ultrasonography, of whom 2946 had interpretable images of the internal carotid artery. Missing data were due to scheduling issues or unavailability of the ultrasonographic device.*
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	NR
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes. *Ultrasonographic images were acquired at end diastole (defined as the R wave of an electrocardiogram) by a sonographer certified by the Registry of Diagnostic Medical Sonographers. Intima–media interface lines were manually traced as continuous lines by a certified reader, and intima–media thickness values were calculated.19 The mean intima–media thickness of the common carotid artery was measured over a segment of the common carotid artery that was 1 cm long, located approximately 0.5 cm below the carotid-artery bulb, and considered not to contain any plaque (i.e., not to have any perceivable protrusion of the artery wall into the lumen). The maximum intima–media thickness of the internal carotid artery was defined as the greatest intima–media thickness in either the right or left internal carotid artery extending from the bulb to 1 cm above the carotid sinus*
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes. *All cardiovascular events in the Framingham Offspring Study cohort were adjudicated by a panel of three physicians, on the basis of a review of data collected from Framingham clinic visits, inpatient hospitalizations, and office records.*
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes. Multivariable Cox proportional-hazards models were generated. The incremental effect of adding intima–media thickness to the Framingham risk score for predicting cardiovascular outcomes was evaluated with the use of the net reclassification index

2.11. Pollak 2013

	Study identification	Pollak 2013[12]
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes. *The MESA is a multiethnic population of 6814 men and women aged 45 to 84 years without evidence of clinical CVD at baseline enrolled between July 2000 and August 2002 at 6 sites in the United States. The MESA cohort includes white, African American, Hispanic, and Chinese participants. Participants were excluded if they had physician diagnosis of heart attack, stroke, transient ischemic attack, heart failure, angina, atrial fibrillation, a history of any cardiovascular procedure, weight >300 lb, pregnancy, or any medical condition that would prevent long-term participation*
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	NR
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes. *The patients were supine with their head rotated 45° toward the side opposite to the side being imaged. A transverse sweep was recorded from the low neck through the carotid artery bifurcation into the ICA. Doppler velocity measurements were made at the site of any bulb or proximal ICA lesion or in the proximal ICA if no lesions were seen. The common carotid artery (CCA) was then imaged at 45° from the vertical with the beginning of the bulb shown to the left of the image. Three views centered on the ICA bulb were taken: 1 anterior, 1 lateral (at 45°), and 1 posterior. A matrix array probe (M12L, General Electric) was used with the frequency set at 13 MHz for the CCA and 9 MHz for the ICA and with 2 focal zones at a frame rate of 32 frames/s. All carotid artery measurements were blinded*
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes. *Events were identified during follow-up examinations and by telephone interview conducted every 9 to 12 months to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. Copies were obtained of all death certificates and of all medical records for hospitalizations and outpatient cardiovascular diagnoses. Two physicians from the MESA study events committee independently reviewed all medical records for end point classification and assignment of incidence dates. The review process included all generated International Classification of Disease definitions but the final adjudication of MESA end points was based on specific criteria applied to data obtained from medical records by 2 committee members or by the whole study events committee in case of disagreement*

1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes. *Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) were calculated as described by Pencina et al.NRI was calculated from the Framingham predicted risk cut points of 6% and 20% at 10 years translating into 4.7% and 15.6% at a mean follow-up of 7.8 years. Sensitivity analyses were performed by adding common carotid IMT to the respective models*

3. SEARCH STRATEGY – ECONOMIC REVIEW

3.1. Medline (OVID)

Date	18-12-2014			**12-01-2015**		
Database	Medline (OVID)			**Medline (OVID)**		
Search Strategy	#	***Query***	***Results***	#	***Query***	*Results*
	1	Exp cardiovascular diseases/	1957219	1	Exp cardiovascular diseases/	**1957219**
	2	Cardiovascular.mp.	395910	2	Cardiovascular.mp.	**395910**
	3	Exp Stroke/ OR stroke.mp.	215014	3	Exp Stroke/ OR stroke.mp.	**215014**
	4	Cerebrovascular.mp.	115471	4	Cerebrovascular.mp.	**115471**
	5	Coronary.mp. OR exp Acute Coronary Syndrome/	412821	5	Coronary.mp. OR exp Acute Coronary Syndrome/	**412821**
	6	Myocardial infarction.mp. OR exp Myocardial Infarction/	204375	6	Myocardial infarction.mp. OR exp Myocardial Infarction/	**204375**
	7	1 OR 2 OR 3 OR 4 OR 5 OR 6	2270159	7	1 OR 2 OR 3 OR 4 OR 5 OR 6	**2270159**
	8	Carotid intima-media thickness.mp. OR Carotid intima-media thickness/	4935	8	Pulse wave velocity.mp.	**4384**
	9	Ankle-brachial index.mp. OR Ankle-brachial index/	3749	9	Arterial stiffness.mp.	**4209**
	10	Liver attenuation.mp.	108	10	“Plaque*”.mp.	**88350**
	11	pericardial adipose tissue.mp.	47	11	Exp Plaque, Atherosclerotic/	**3110**
	12	(calcium OR calcinosis OR calcification).mp.	553843	12	8 OR 9 OR 10 OR 11	**95169**
	13	Inter-arm blood pressure difference.mp.	13	13	exp Economics/	**513380**
	14	brachial flow-mediated dilation.mp.	109	14	exp Health Care Costs/	**49630**
	15	8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14	561905	15	exp Economics, Medical/	**14043**

	16	exp Economics/	513380	16	(cost or cost analysis).mp.	**349437**
	17	exp Health Care Costs/	49630	17	exp Economics, Pharmaceutical/	**2645**
	18	exp Economics, Medical/	14043	18	exp Economics, Hospital/	**20284**
	19	(cost or cost analysis).mp.	349437	19	exp Economics, Nursing/	**4026**
	20	exp Economics, Pharmaceutical/	2645	20	Value of Life/	**6025**
	21	exp Economics, Hospital/	20284	21	("cost effectiveness" or cost-effectiveness).mp.	**38397**
	22	exp Economics, Nursing/	4026	22	exp Quality-Adjusted Life Years/	**7642**
	23	Value of Life/	6025	23	("cost utility" or cost-utility).mp.	**2723**
	24	("cost effectiveness" or cost-effectiveness).mp.	38397	24	exp Health Expenditures/	**16589**
	25	exp Quality-Adjusted Life Years/	7642	25	16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27	**693664**
	26	("cost utility" or cost-utility).mp.	2723	26	7 AND 12 AND 25	**252**
	27	exp Health Expenditures/	16589	27	Limit 26 to yr=”2008-Current”	**100**
	28	16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27	693664			
	29	7 AND 15 AND 28	1195			
	30	**limit 29 to yr="2008 -Current"**	**446**			

3.2. EMBASE

Date	18-12-2014			**12/01/2015**		
Database	EMBASE			**EMBASE**		
Search Strategy	**#**	***Query***	***Results***	**#**	***Query***	*Results*
	1	'cardiovascular disease' AND (embase)/lim	202851	1	'cardiovascular disease' AND (embase)/lim	**204510**
	2	Cardiovascular:ab,ti AND (embase)/lim	340827	2	Cardiovascular:ab,ti AND (embase)/lim	**343363**
	3	Stroke:ab,ti AND (embase)/lim	196037	3	Stroke:ab,ti AND (embase)/lim	**197431**
	4	Cerebrovascular:ab,ti AND (embase)/lim	44255	4	Cerebrovascular:ab,ti AND (embase)/lim	**44518**
	5	Coronary:ab,ti AND (embase)/lim	347436	5	Coronary:ab,ti AND (embase)/lim	**348969**
	6	'Myocardial infarction':ab,ti AND (embase)/lim	159935	6	'Myocardial infarction':ab,ti AND (embase)/lim	**160687**
	7	1 OR 2 OR 3 OR 4 OR 5 OR 6	920588	7	1 OR 2 OR 3 OR 4 OR 5 OR 6	**926180**
	8	'Arterial wall thickness'/exp AND (embase)/lim	10902	8	'Pulse wave velocity':ab,ti AND (embase)/lim	**8006**
	9	'Ankle-brachial index'/exp AND (embase)/lim	5406	9	'Arterial stiffness':ab,ti AND (embase)/lim	**7832**
	10	'Ankle-brachial index':ab,ti AND (embase)/lim	3920	10	Plaque*:ab,ti AND (embase)/lim	**98485**
	11	'Liver attenuation':ab,ti AND (embase)/lim	156	11	'atherosclerotic plaque'/exp AND (embase)/lim	**8223**
	12	'pericardial adipose tissue' AND (embase)/lim	97	12	8 AND 9 AND 10 AND 11	**109616**
	13	(calcium OR calcinosis OR calcification) AND (embase)/lim	577472	13	'economics'/exp AND [embase]/lim	**17768**
	14	('inter-arm blood pressure difference' OR 'brachial-brachial index') AND (embase)/lim	27	14	'cost benefit analysis'/exp AND [embase]/lim	**45159**
	15	'brachial flow-mediated dilation' AND (embase)/lim	132	15	'cost effectiveness analysis'/exp AND	**102536**
	16	8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15	592749	16	'cost utility analysis'/exp AND [embase]/lim	**5855**
	17	'economics'/exp AND [embase]/lim	17,706	17	'cost minimization analysis'/exp AND [embase]/lim	**2577**

	18	'cost benefit analysis'/exp AND [embase]/lim	44,941	18	'quality adjusted life year'/exp AND [embase]/lim	**11985**
	19	'cost effectiveness analysis'/exp AND	101,844	19	13 AND 14 AND 15 AND 16 AND 17 AND 18	**162960**
	20	'cost control'/exp AND [embase]/lim	31,376	20	19 AND (2008-2015)/py	**83**
	21	'cost utility analysis'/exp AND [embase]/lim	5,800			
	22	'cost minimization analysis'/exp AND [embase]/lim	2,572			
	23	'quality adjusted life year'/exp AND [embase]/lim	11,823			
	24	17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23	183294			
	25	7 AND 16 AND 24	1080			
	26	**25 AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py)**	**501**			

3.3. NHSEED & NHSHTA (CRD)

Date: **18-12-2014**

Database: **NHSEED & NHSHTA (CRD)**

#	*Query*	*Results*
1	MeSH DESCRIPTOR Cardiovascular Diseases EXPLODE ALL TREES	9973
2	(cost*) IN NHSEED, HTA FROM 2008 TO 2015	9019
3	(calcium OR calcinosis OR calcification) IN NHSEED, HTA FROM 2008 TO 2015	83
4	((pulse wave velocity)) IN NHSEED, HTA FROM 2008 TO 2015	0
5	((plaque OR (atherosclerotic plaque))) IN NHSEED, HTA FROM 2008 TO 2015	57
6	((arterial stiffness)) IN NHSEED, HTA FROM 2008 TO 2015	0
5	#3 OR #4 OR #5 OR #6	138
6	#1 AND #2 AND #5	19

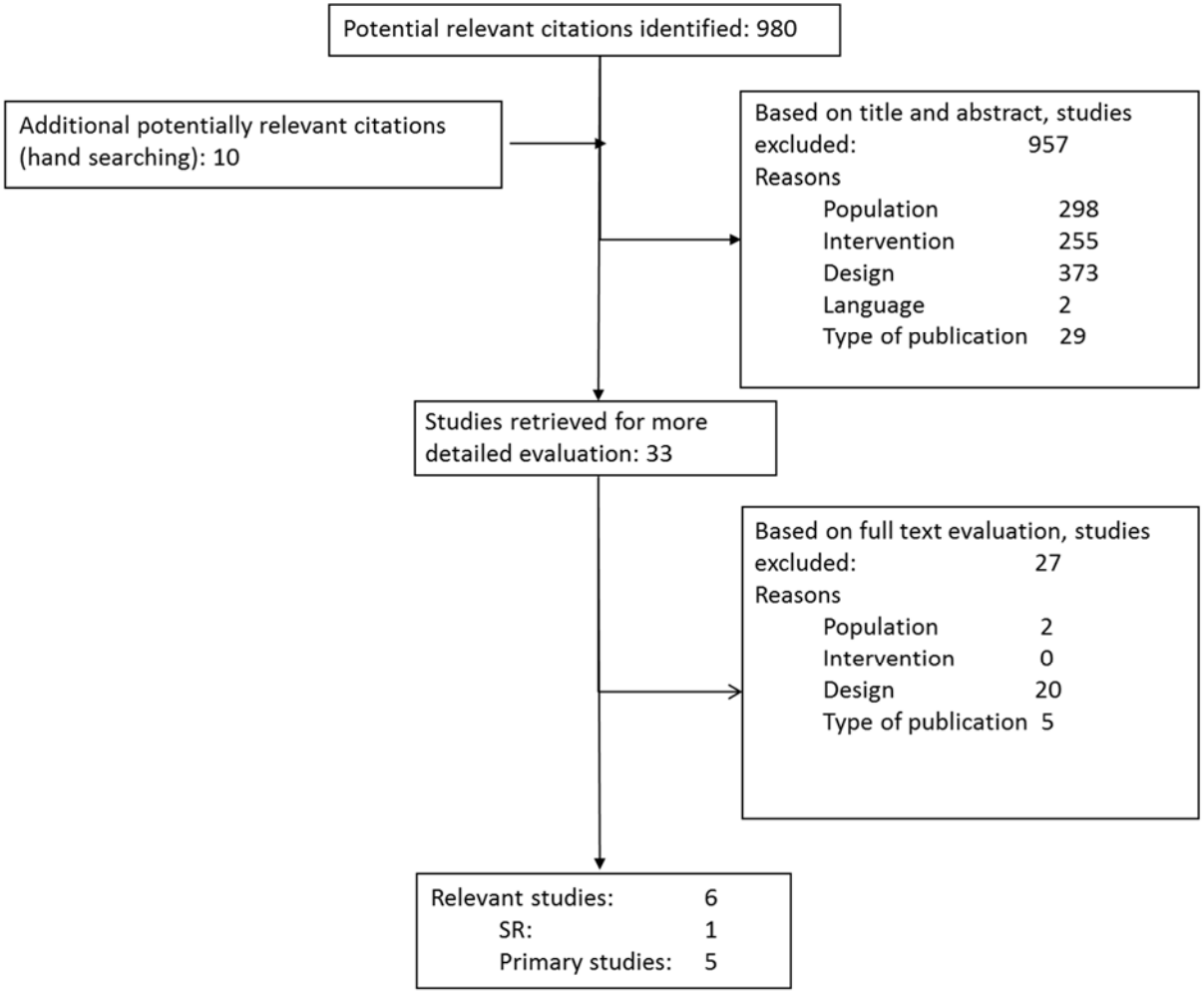
3.4. Econlit

Date: **18-12-2014**

Database: **EconLit**

#	*Query*	*Results*
1	cardiovascular disease.mp.	102
2	calcium.mp.	78
3	pulse wave velocity.mp.	1
4	plaque.mp.	4
5	2 or 3 or 4	83
6	1 and 5	2

4. FLOW CHART SELECTION - ECONOMIC EVALUATIONS



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