



Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review

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ABSTRACT

Context Imaging for subclinical atherosclerosis on top of conventional risk factor assessment may improve risk prediction for the occurrence of cardiovascular disease events in asymptomatic individuals.

Objective To systematically review the available evidence on this issue.

Data Sources PubMed MEDLINE was systematically searched on 7 September 2011.

Study selection Studies were included that evaluated the added value of flow mediated dilation (FMD), carotid intima-media thickness (CIMT), carotid plaques and/or coronary artery calcification (CAC) scoring in the prediction of risk for developing fatal or non-fatal cardiovascular events.

Data extraction Data on general study characteristics and the added predictive performance of imaging markers in terms of discrimination, calibration and (re)classification were extracted.

Results 25 studies were selected that provided information on added predictive value of FMD (n=2), CIMT (n=12), carotid plaques (n=6) and/or CAC (n=9). Heterogeneity existed across studies in the conventional risk models that were used and in the measurements of the imaging marker. The added predictive value, quantified by the difference in c-index, of FMD, CIMT, carotid plaques or CAC ranged from 0.00 to 0.01 for FMD, from 0.00 to 0.03 for CIMT, from 0.01 to 0.05 for carotid plaque and from 0.05 to 0.13 for CAC. The reported net reclassification improvement (NRI) by the imaging markers ranged from -1.4% to 12% for CIMT, 8% to 11% for carotid plaques, 14% to 25% for CAC and 29% for FMD). Although the definition of intermediate cardiovascular risk varied across studies, the NRI was the highest in those at intermediate cardiovascular risk.

Conclusions Published evidence on the added value of atherosclerosis imaging varies across the different markers, with limited evidence for FMD and considerable evidence for CIMT, carotid plaque and CAC. The added predictive value of additional screening may be primarily found in asymptomatic individuals at intermediate cardiovascular risk. Additional research in asymptomatic individuals is needed to quantify the cost effectiveness and impact of imaging for subclinical atherosclerosis on cardiovascular risk factor management and patient outcomes.

INTRODUCTION

Atherosclerosis is the underlying cause of the majority of cardiovascular disease (CVD) events. CVD is the leading cause of morbidity and mortality in the western world.¹ Risk factors for atherosclerosis and CVD, including age, sex, lipid

levels, smoking and blood pressure, are incorporated in risk algorithms that are used to predict an individual's absolute risk for CVD in the general population.² Although these risk factors are useful to predict risk in populations, their accuracy in predicting cardiovascular risk in individuals varies considerably across populations.³ As atherosclerosis may be considered as the sum of the effects of exposure to known and unknown risk factors within an individual, its measurement may be sensible to improve the identification of individuals at high risk for CVD leading to efficient preventive strategies in these high risk individuals.⁴

Several non-invasive approaches allow measurement of atherosclerosis from early to late stages of the disease. B mode ultrasound is commonly used to assess brachial artery flow mediated dilation (FMD), carotid intima-media thickness (CIMT) and carotid plaques, whereas coronary artery calcification (CAC) score is examined through electron beam or multislice CT. Unfavourable values of FMD, CIMT, carotid plaques and CAC have all been associated with an increased risk of development of CVD, independent of established cardiovascular risk factors.⁵⁻⁸ Traditional risk assessment extended with assessment of FMD, CIMT, carotid plaques or CAC may improve the risk classification of individuals without known CVD compared with traditional risk factors only but definite evidence is not yet available.⁹⁻¹¹

To summarise the existing body of evidence, to identify potential gaps in the existing knowledge and to serve as a guide for future studies, we systematically reviewed the available literature for 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.

METHODS

Eligibility criteria and selection of studies

A systematic search was performed at PubMed MEDLINE (<http://www.ncbi.nlm.nih.gov>) on 7 September 2011 using the strings described in table 1. Based on title and abstract, 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.

The markers of subclinical atherosclerosis that were eligible for inclusion were FMD, CIMT,

Table 1 Description of the search strategy used to identify publications of interest

Database	PubMed on 7 September 2011
General	Only English language
Domain	#1: incidence[Title/Abstract] OR prognos*[Title/Abstract] OR predict*[Title/Abstract] #2: reclassi*[Title/Abstract] reclassification[Title/Abstract] OR net reclassification index[Title/Abstract] OR net reclassification improvement[Title/Abstract] OR NRI[Title/Abstract] OR ROC-curve[Title/Abstract] OR AUC[Title/Abstract] OR area under the curve[Title/Abstract] OR receiver operating characteristic curve[Title/Abstract] OR c-index[Title/Abstract] OR receiver operating characteristic[Title/Abstract] OR concordance index[Title/Abstract] OR ROC[Title/Abstract] OR positive predictive value[Title/Abstract] OR negative predictive value[Title/Abstract] OR sensitivity[Title/Abstract] OR specificity[Title/Abstract]
Predictive factor	#3: coronary artery calcification[Title/Abstract] OR CAC[Title/Abstract] OR coronary artery calcium[Title/Abstract] OR coronary calcification[Title/Abstract] OR calcification[Title/Abstract] OR coronary arterial calcification[Title/Abstract] OR arterial calcification[Title/Abstract] OR calcium score[Title/Abstract] OR coronary computed tomographic angiography [Title/Abstract] OR CCTA [Title/Abstract] #4: carotid*[Title/Abstract] OR IMT [Title/Abstract] OR intimal medial thickness [Title/Abstract] OR Intima media thickness[Title/Abstract] #5: plaque*[Title/Abstract] OR plaque volume[Title/Abstract] OR plaque size[Title/Abstract] OR atherosclerotic plaque[Title/Abstract]) #6: FMD[ti/ab] OR brachial FMD [ti/ab] OR flow-mediated vasodilatation[ti/ab] OR flow-mediated vasodilatation[ti/ab] OR flow-mediated dilatation[ti/ab] OR vasodilation[ti/ab] OR flow-mediated[ti/ab] OR endothelium[ti/ab] OR brachial artery[ti/ab] OR vasodilatation[ti/ab] OR endothelial dysfunction[ti/ab] OR brachial reactivity[ti/ab]
Outcome	#7: risk*[Title/Abstract] NOT risk factors[Title/Abstract] OR cardiovascular disease[Title/Abstract] OR mortality[Title/Abstract] OR cardiovascular death[Title/Abstract] OR predict[Title/Abstract] OR coronary heart disease[Title/Abstract] OR cerebrovascular disease[Title/Abstract] OR stroke[Title/Abstract] OR myocardial infarction[Title/Abstract] OR events[Title/Abstract]
Search results	#1: 1 361 034 hits #2: 658 141 hits #3: 29 000 hits #4: 809 88 hits #5: 79 158 hits #6: 21 150 hits #7: 1 672 619 hits #1 and #2 and (#3 or #4 or #5 or #6) and #7: 1122 hits

carotid plaques and CAC. FMD measurement evaluates the function of the endothelium in the brachial artery, and abnormal values representing endothelial dysfunction are considered to be the first stage of atherosclerosis.¹² CIMT is a structural anatomical measure of the thickness of the arterial wall which is used to detect early to late stages of subclinical atherosclerosis.¹³ Carotid plaques generally represent an advanced stage of atherosclerosis and are focal structures in the arterial wall that intrude into the lumen or areas of a homogeneously severely thickened arterial wall. Late stages of the atherosclerotic process reflect calcium in the vessel wall, and for the coronary arteries this can be measured by CAC.¹⁴

The outcomes of interest were fatal and non-fatal cardiovascular events. The domain comprised individuals without symptomatic CVD and without diabetes mellitus as many general cardiovascular prediction models are most likely to be applied in these individuals.

Data extraction

Publications were reviewed in duplicate (by SAEP and HMR) and the references of the selected studies were examined.

General characteristics together with the definitions of the used traditional prediction model, the imaging marker of atherosclerosis and the outcome measures were extracted from each eligible study.

Data on the predictive performance of the prediction models in terms of discrimination, calibration and (re)classification were also extracted. Calibration describes the agreement between the predicted probabilities based on the prediction model and the actual observed probabilities. Discrimination describes the overall ability of a prediction model to distinguish between individuals that will or will not experience an event. Calibration was assessed using published results on goodness of fit tests. Overall discrimination was assessed using change in the c-statistic. The c-statistic quantifies the ability of a prediction model to discriminate between individuals with or without an event by giving a higher predicted probability to individuals experiencing an event compared with individuals not experiencing an event. Finally, the net reclassification improvement in the total population and in intermediate risk individuals (NRI_{overall} and NRI_{intermediate}), and the integrated discrimination

improvement (IDI), were retrieved. The NRI_{overall} reflects the percentage of individuals in the total population that are correctly reclassified into clinically meaningful higher or lower prespecified risk categories with the addition of a new marker to the risk algorithm. The NRI_{intermediate} specifically focuses on intermediate risk individuals, the group in whom treatment decisions may be the most uncertain, and reflects the proportion of up and down classifications to lower or higher risk categories in individuals considered as intermediate risk using the traditional prediction model. The definitions of the risk groups used to estimate the NRI (overall and intermediate) were also retrieved as they could differ across studies.¹⁵ Correct reclassifications are shifts to a higher risk category in cases and shifts to a lower risk category in non-cases. The IDI estimates the improvement of the basic prediction model in the average sensitivity after addition of the new imaging marker subtracted by any increase in the mean 1–specificity.¹⁵

Quality appraisal and heterogeneity

In contrast with randomised therapeutic and diagnostic (single) test accuracy studies, there are unfortunately no agreed, let alone established, criteria for quality appraisal of primary prognostic studies.¹⁶ However, we assessed the quality of the included studies starting from methodological guidelines for predictive studies and previously used quality criteria in reviews of prognostic studies.^{16–20} The items that we scored per article are listed in supplementary table 2 (available online only).

To obtain some indication of whether publication bias could be present, we plotted the sample size of each study against the corresponding change in c-statistic after addition of the new marker found in that study. These plots were subsequently used to examine the presence of extraordinary changes in c-statistic relative to other studies on the same marker.

The heterogeneity between studies was further assessed to determine whether a formal meta-analysis was possible. Large heterogeneity was present across studies in terms of definition of the baseline prediction model, definition of the marker of atherosclerosis and study outcomes. Also, vital data on the precision of the point estimates were frequently not reported. The data extracted were therefore not suitable to perform a formal meta-analysis beyond the systematic review.

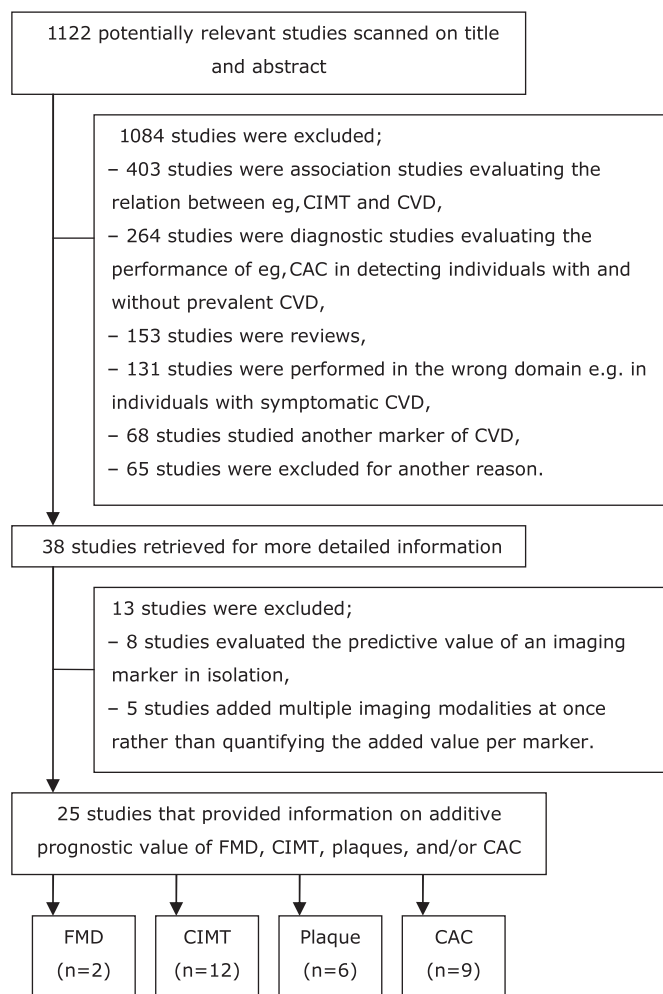


Figure 1 Flowchart of selection of articles. CAC, coronary artery calcification; CIMT, carotid intima–media thickness; CVD, cardiovascular disease; FMD, flow mediated dilation.

RESULTS

Figure 1 shows the flowchart of the selection of articles. Our initial search (table 1) resulted in 1122 studies that were potentially relevant. After reviewing titles and abstracts, 38 articles were evaluated using full text, yielding another 13 excluded studies. Of the final 25 studies, two studies used FMD as a marker to improve risk prediction,^{11 21} 12 studies used CIMT,^{9 22–32} six studies used carotid plaques^{9 23 28 33–35} and nine studies used CAC.^{10 27 36–42} The baseline prediction models used in each of these studies are described in supplementary table 1 (available online only). The quality assessment of the included studies is shown in supplementary table 2 (available online only). The studies described the majority of quality appraisal items. Only the reasons for loss to follow-up and the presence of missing data in the predictive marker and/or outcome of interest were poorly reported.

The change in c-statistic for studies on FMD, CIMT and carotid plaques ranged from 0.00 to 0.05 without a clear association with study size, or a particularly influential single study (figure 2). For CAC, changes in c-statistic generally ranged from 0.04 to 0.09 although one study showed a large change in c-statistic of 0.13 which was also a relatively small study (n=676).

Flow mediated dilation

The definition of FMD was comparable across the three studies (table 2). Calibration was not assessed in any of the studies on

the added predictive value of FMD. In the Cardiovascular Health Study and Multi-Ethnic Study of Atherosclerosis (MESA), no changes in the c-statistic were reported after the addition of FMD to the basic prediction model (table 2).^{11 21}

The $NRI_{overall}$ in MESA showed that the addition of FMD to the model reclassified 29% of the individuals in appropriate risk categories ($p<0.0001$), and was most apparent in those at intermediate risk ($NRI_{intermediate}$ 28%, $p<0.0001$, table 2). The authors concluded that these results need to be replicated in other cohorts and that the interobserver and intraobserver variability of FMD measurements should decrease before implementation of FMD as a formal screening tool for CVD risk could be justified.

Carotid intima–media thickness

Various definitions for CIMT and cut-offs for intermediate cardiovascular risk were used across the 12 included studies (table 3). Calibration was assessed in four studies.^{9 22 23 30} Both the original and extended models showed good agreement between the observed and predicted probabilities in two of the four studies.^{22 23} The c-statistic of the prediction models without CIMT increased from 0.00 to 0.03 when CIMT was added.

In the Atherosclerosis Risk In Communities (ARIC) study, addition of CIMT to the prediction model resulted in an $NRI_{overall}$ of 7.1% (95% CI 2.2% to 10.6%) and an IDI of 0.007 (95% CI 0.004 to 0.010). The $NRI_{intermediate}$ was 16.7% (95% CI 9.3% to 22.4%).⁹ In contrast, 10 year results from the Carotid Atherosclerosis Progression Study showed that addition of CIMT to the prediction model resulted in an IDI of 0.04% and $NRI_{overall}$ of –1.41%.³⁰ Analysis of 1574 participants from the Firefighters and Their Endothelium study showed an $NRI_{overall}$ of 11.6% ($p=0.044$) and an $NRI_{intermediate}$ of 18.0% ($p=0.034$).²²

Carotid plaque

The definition of carotid plaque and of intermediate cardiovascular risk varied across the six included studies (table 4). Calibration was good in the only study that reported the goodness of fit test results for both the traditional prediction model and the extended version of the model.²³ The c-statistic of the traditional models increased from 0.01 to 0.06 after addition of carotid plaque.

A recent publication from the ARIC study showed that the $NRI_{overall}$ was 7.7% (95% CI 2.3% to 11.4%) and the IDI was 0.0008 (95% CI 0.005% to 0.012%) when the presence or absence of plaque was added to the traditional prediction model.⁹ The $NRI_{intermediate}$ was 17.7% (95% CI 10.9% to 24.7%). Also, a Chinese cohort study showed that plaque assessment led to an $NRI_{overall}$ of 10.5% (95% CI 9.4% to 11.6%) of the individuals.³⁵

CAC Score

The definition of CAC was fairly consistent across the nine included studies but the definition of intermediate cardiovascular risk differed between studies (table 5). Calibration improved with addition of CAC in one study³⁸ whereas both the original and extended models had a good fit in two other studies.^{10 40} The c-statistic increased from 0.04 to 0.13 when CAC was added to the model.

Four recently published studies also reported results on the NRI and/or the IDI.^{10 37 38 40} One of these studies comprised a subgroup analysis of an earlier publication in the total population in individuals without indications for statin therapy.^{38 40} Analyses of the MESA study showed that addition of CAC to the conventional prediction model resulted in an $NRI_{overall}$ of 25% (95% CI 16% to 34%) and an $NRI_{intermediate}$ of 55% (95% CI 41%

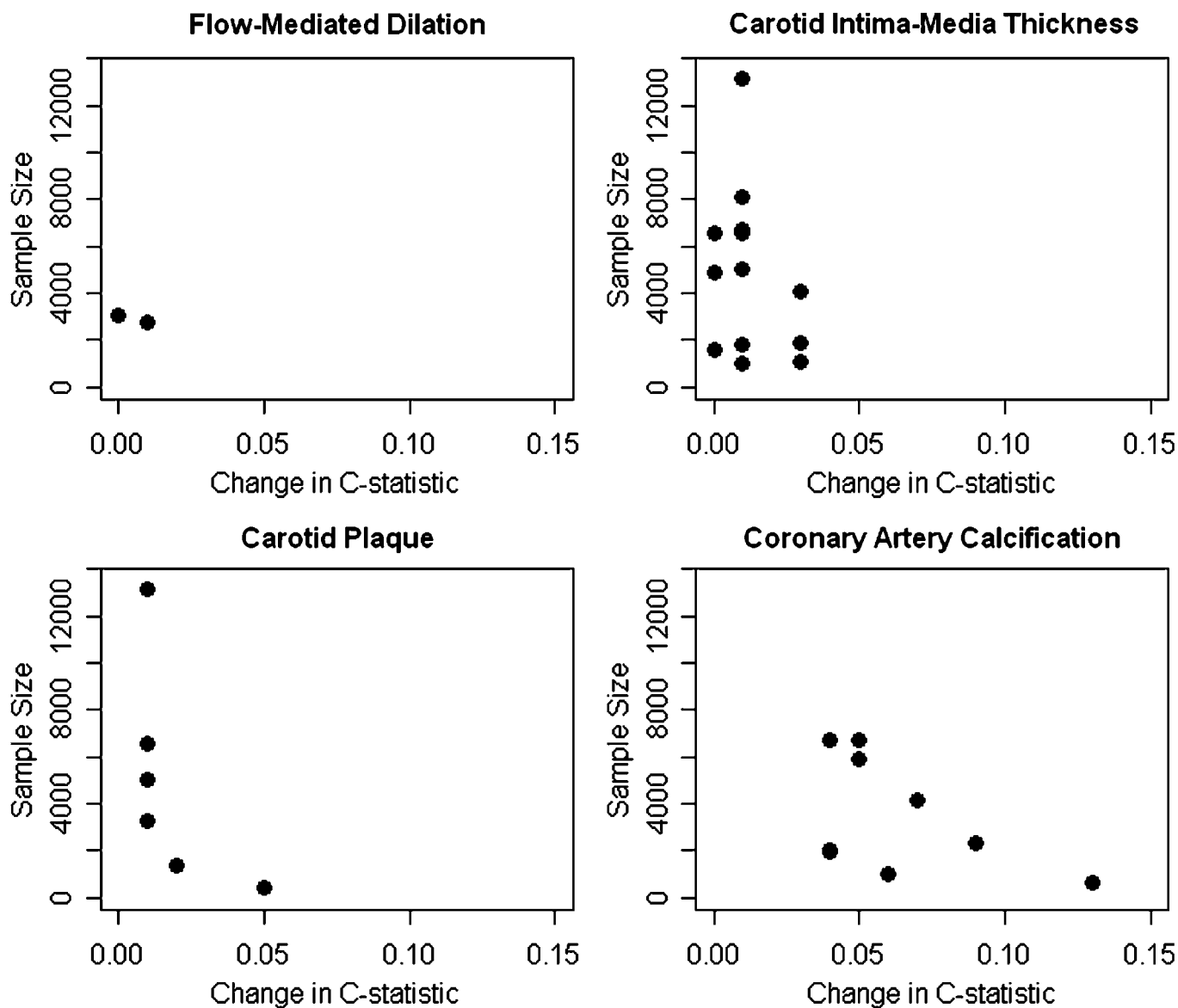


Figure 2 Association between sample size and change in c-statistic after addition of the imaging marker across studies.

to 69%).¹⁰ The IDI in the MESA study was 0.026. Results were similar in the Rotterdam study.³⁷ Addition of CAC to the prediction model led to an $\text{NRI}_{\text{overall}}$ of 14% ($p < 0.01$) which was mainly driven by correctly reclassifying those at intermediate risk according to the traditional prediction model. Results from the Heinz Nixdorf Recall study also showed large NRIs when CAC was added to the Framingham Risk Score.³⁸ Using different thresholds to define the intermediate risk category (10–20% or 6–20%), the $\text{NRI}_{\text{overall}}$ was 22% and 20%, respectively. The $\text{NRI}_{\text{intermediate}}$ was 22% for intermediate risk thresholds of 10–20% and 31% for intermediate risk thresholds of 6–20%. In addition, the IDI was 0.0152 when the prediction models with and without CAC were compared. The $\text{NRI}_{\text{overall}}$ was 25.1% and the IDI was 0.0167 in individuals from the Heinz Nixdorf Recall study without indications for statin therapy.⁴⁰ However, the authors did not recommend the use of CAC in this low risk population given an event rate of 2.2% over 5 years of follow-up.

DISCUSSION

The published evidence on added value atherosclerosis imaging in cardiovascular risk prediction varies across markers. For FMD,

the evidence for added value is limited whereas the evidence for CIMT, carotid plaque and CAC is considerable. Individuals at intermediate risk for CVD according to traditional risk factor assessment may benefit most from additional imaging for subclinical atherosclerosis.

Risk prediction is most likely to be improved by means of carotid ultrasound measurements to determine CIMT or carotid plaque, or CAC. CIMT measurements extended with assessment of carotid plaques may increase the potential for identifying subclinical vascular disease.⁴⁴ Indeed, the combination of CIMT and carotid plaque has been shown to improve the prediction of ischaemic CVD compared with CIMT or carotid plaque alone.^{9, 45} Direct comparisons between carotid ultrasound and CAC or the predictive performance of the combination of these imaging modalities, however, have not been made. Nevertheless, although carotid ultrasound is feasible in all individuals, relatively inexpensive and without exposure to radiation, CAC represents a later stage of atherosclerosis, involves a risk of cancer due to radiation exposure and may be uninformative in younger individuals because of the zero calcium scores.⁴⁶ It has been shown that CIMT is thicker in individuals

Table 2 General study characteristics and the estimated added predictive value of flow mediated dilation on top of traditional risk factor assessment

First author	Year	Region	N	Mean age (years)	% Men	FU (years)	Definition marker	Endpoint	Event rate (%)	C-statistic without FMD	C-statistic with FMD	NRI (%)*
Yeboah ²¹	2007	USA	2792	79	41	5	% change in arterial diameter 2 min after cuff deflation and baseline	CVD†	24.1	0.65	0.66	—
Yeboah ¹¹	2009	USA	3026	61	50	5	% change in arterial diameter 2 min after cuff deflation and baseline	CVD†	6.0	0.74	0.74	29

The baseline prediction model used in each of the studies is described in supplementary table 1 (available online only).

*Intermediate risk was defined as an absolute predicted 5 year risk between 4% and 7.5%.¹¹

†Non-fatal and fatal events.

CVD, cardiovascular disease; FMD, flow mediated dilation; FU, follow-up; NRI, net reclassification improvement.

with zero or low CAC having an event compared with those without event.^{47–48} Also, a recent study showed that while 47% of the young to middle-aged individuals with a low Framingham Risk Score with CAC of zero had evidence of subclinical atherosclerosis in the carotid artery, only 15% of those with a low CIMT had detectable CAC.⁴⁹ Therefore, carotid ultrasound may be a better screening tool to assess cardiovascular risk in low risk populations than CAC.

Recommendations from recent guidelines

A number of guidelines have addressed the use of imaging for subclinical atherosclerosis as a tool to improve risk prediction.^{44–50–52} A recent systematic review of guidelines on imaging for individuals with asymptomatic coronary artery disease included 14 guidelines that addressed the use of CAC in risk assessment.⁵⁰ The recommendations of these guidelines varied; one guideline recommended its use, four guidelines considered the use of CAC in risk prediction and nine guidelines did not recommend its use or found insufficient evidence to justify its

use.⁵⁰ On the contrary, the Society for Heart Attack Prevention and Eradication guideline recommends periodic measurement of CAC or carotid ultrasound of CIMT and plaque in all asymptomatic men aged 45–75 years and women aged 55–75 years, excluding those defined as very low risk.⁵² This recommendation is driven by the principle that the presence of the underlying disease itself—that is, subclinical atherosclerosis—is the major causal risk factor for CVD in asymptomatic individuals rather than a prominent additional predictive factor.¹⁵ The recently published 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults recommends that risk assessment using existing risk prediction models are extended with information on family history for CVD as a first step.⁵¹ Individuals at low or high risk according to this initial risk assessment do not require further testing as this is not expected to lead to a change in treatment decisions. However, additional testing may be useful to guide therapy for those at intermediate risk.⁵¹ Although FMD measurements are not recommended in the 2010 ACCF/AHA guideline and the use of carotid plaque is

Table 3 General study characteristics and the estimated added predictive value of carotid intima–media thickness on top of traditional risk factor assessment

First author	Year	Region	N	Mean age (years)	% Men	FU (years)	Definition marker	Endpoint	Event rate (%)	C-statistic without CIMT	C-statistic with CIMT	NRI (CI) (%)*
Anderson ²²	2011	Canada	1574	49	100	7	Mean CCA, r	CVD‡	4.5	0.75	0.75	11.6
Cao ²³	2007	USA	5020	73	40	8	meanmx CCA and ICA, nfw, lr	CVD‡	37.9	0.72	0.73	—
Chambless ²⁴	2003	USA	14 054	45–64	43	10	Mean CCA, BIF, ICA fw, lr	CHD‡	7.5	Bl. women: 0.83 Wh. women: 0.79 Bl. men: 0.66 Wh. men: 0.68 Men: 0.76 Women: 0.80	Bl. women: 0.84 Wh. women: 0.80 Bl. men: 0.69 Wh. men: 0.71 Men: 0.77 Women: 0.81	—
Chambless ²⁵	2004	USA	14 685	45–64	45	12	Mean CCA, BIF, ICA fw, lr	Stroke†	3.0	Men: 0.76 Women: 0.80	Men: 0.77 Women: 0.81	—
Elias-Smale ³¹	2011	The Netherlands	3580	65	39	12	Mean CCA, nfw, lr	CHD and stroke‡	14.8	CHD, stroke: Men: 0.61, 0.69 Women: 0.71, 0.71	CHD, stroke: Men: 0.61, 0.70 Women: 0.72, 0.72	CHD, stroke: Men: 0.2, 3.9 Women: 8.2, 8.0
Folsom ²⁷	2008	USA	6698	45–84	47	4	Z score sum max CCA, ICA, nfw, lr	CVD‡	3.3	0.77	0.78	—
Lorenz ³⁰	2010	Germany	4909	50	48	10	Mean CCA, BIF, ICA, fw, lr	CVD‡	7.6	0.72	0.72	–1.4
Mathiesen ²⁸	2011	Norway	6584	60	49	10	Mean CCA, fw	Stroke‡	6.0	0.74	0.74	—
Nambi ⁹	2010	USA	13 145	54	43	15	meanmn CCA, BIF, ICA, fw, lr	CHD‡	13.7	0.74	0.75	7.1 (2.2 to 10.6)
Polak ³²	2011	USA	2965	58	45	8	Mean CCA, and max ICA	CVD‡	10.0	0.75	CCA: 0.75 ICA: 0.76	CCA: 0.0 ICA: 7.6
Price ²⁹	2007	UK	1007	69	48	12	Max CCA, fw, lr	CVD†	24.7	0.61	0.62	—
del Sol ²⁶	2001	The Netherlands	1881	71	41	4	Max CCA, nfw lr	CVD‡	NA	0.72	0.75	—

The baseline prediction model used in each of the studies is described in supplementary table 1 (available online only).

*Intermediate risk was defined as an absolute 5 year risk between 5% and 20%,²² a 10 year risk between 5% and 10% and 10% and 20%^{9–30} or a 10 year risk between 10% and 20%.³¹

†Non-fatal and fatal events.

‡Non-fatal and fatal events.
BIF, carotid bifurcation; Bl., black; CCA, common carotid artery; CHD, coronary heart disease; CIMT, carotid intima–media thickness; CVD, cardiovascular disease; FU, follow-up; fw, far wall of the carotid artery; ICA, internal carotid artery; lr, left and right carotid artery; meanmn, mean of the mean segment specific CIMT measurement; meanmx, mean of the maximal segment specific CIMT measurement; nfw, near and far wall of the carotid artery; NRI, net reclassification improvement; r, right carotid artery; Wh., white.

Table 4 General study characteristics and the estimated added predictive value of carotid plaque on top of traditional risk factor assessment

First author	Year	Region	N	Mean age (years)	% Men	FU (years)	Definition marker	Endpoint	Event rate, (%)	C-statistic without plaque	C-statistic with plaque	NRI (CI), %*
Cao ²³	2007	USA	5020	73	40	8	No, intermediate risk, or high risk plaque	CVD‡	37.9	0.72	0.73	—
Mathiesen ²⁸	2011	Norway	6584	60	49	10	Sum of all plaque areas	Stroke‡	6.0	0.74	0.75	—
Nambi ⁹	2010	USA	13 145	54	43	15	Carotid plaque	CHD‡	13.7	0.74	0.75	7.7 (2.3 to 11.4)
Prati ³³	2011	Italy	1348	18–99	47	12	Total plaque risk score	TIA, stroke, and vascular death‡	8.5	0.88	0.90	—
Stork ³⁴	2006	The Netherlands	403	78	100	4	Sum of all plaque areas	CVD†	7.7	0.67	0.72	—
Xie ³⁵	2011	China	3258	59	41	5	Sum of segments with plaque ⁴³	CHD and stroke‡	4.2	0.74	0.75	10.5 (9.4 to 11.6)

The baseline prediction model used in each of the studies is described in supplementary table 1 (available online only).

*Intermediate risk was defined as an absolute predicted 10 year risk between 5% and 10% and 10% and 20%,⁹ or a 5 year predicted risk between 3% and 10%.³⁵

†Fatal events.

‡Non-fatal and fatal events.

CHD, coronary heart disease; CVD, cardiovascular disease; FU, follow-up; NRI, net reclassification improvement; TIA, transient ischaemic accident.

not addressed, measurement of CIMT and CAC is considered reasonable for risk assessment in asymptomatic individuals at intermediate risk. Measurement of CAC may also be reasonable for screening purposes in individuals at low to intermediate risk.⁵¹ A recent consensus statement from the American Society of Echocardiography for the use of carotid ultrasound to identify subclinical atherosclerosis recommended carotid ultrasound screening in those at intermediate risk for CVD without established CVD and diabetes mellitus.⁴⁴ Ultrasound imaging in individuals with established atherosclerotic vascular disease or in those in whom the results would not be expected to alter therapy is discouraged. The guideline recommends that the ultrasound protocol be restricted to assessment of the far wall of the common carotid artery, supplemented by a thorough scan of the common carotid artery, carotid bifurcation and internal carotid artery to assess the presence of carotid plaque.⁴⁴ The ARIC study recently evaluated the performance of this ultrasound protocol and showed that risk prediction was improved in a manner comparable with the combination of carotid plaque and CIMT measurement in all carotid segments.⁵³

In summary, although current guidelines on the use of imaging for asymptomatic atherosclerosis contain conflicting recommendations, the majority of guidelines point towards the

usefulness of carotid ultrasound measurements of CIMT and plaque, or CAC, in risk prediction for the development of cardiovascular events. Individuals that are classified at intermediate risk using traditional risk factor assessment are considered as the most appropriate subgroup in which further testing is indicated. These recommendations are in agreement with the findings of the present systematic review which also showed that intermediate risk individuals may benefit most from additional risk assessment using CIMT, carotid plaque or CAC.

Future perspective

This systematic review together with the current guidelines indicate that imaging for subclinical atherosclerosis may improve risk stratification for the development of CVD. However, the evidence differs by marker and although adding a marker of atherosclerosis to current prediction models may shift asymptomatic individuals to more appropriate risk categories, evaluation on the clinical benefits of imaging guided risk prediction is lacking.

For FMD the body of evidence is currently limited and at least further prospective cohort studies are required aimed at quantifying whether FMD measurements may indeed improve current prediction models, using state of the art methods in

Table 5 General study characteristics and the estimated added predictive value of coronary artery calcification score on top of traditional risk factor assessment

First author	Year	Region	N	Mean age (years)	% Men	FU (years)	Definition marker	Endpoint	Event rate (%)	C-statistic without CACS	C-statistic with CACS	NRI (CI) (%)*
Detrano ³⁶	2008	USA	6722	62	47	4	Mean CACS	CHD†	2.4	Major: 0.79 Any: 0.77	Major: 0.83 Any: 0.82	—
Elias-Smale ³⁷	2010	The Netherlands	2028	70	43	9	ln(CACS+1)	CHD†	6.7	0.72	0.76	14
Erbel ³⁸	2010	Germany	4129	59	47	5	ln(CACS+1)	CHD†	2.3	0.68	0.75	22.4
Folsom ²⁷	2008	USA	6698	45–84	47	4	Mean CACS	CVD†	3.3	0.77	0.81	—
Greenland ³⁹	2004	USA	1029	66	90	7	CACS	CHD†	5.8	0.63	0.69	—
Mohlenkamp ⁴⁰	2011	Germany	1934	57	31	5	Sum CACS	CVD†	2.2	0.72	0.76	25
Polonsky ¹⁰	2010	USA	5878	62	46	6	Mean CACS	CHD†	3.6	0.76	0.81	25 (16 to 34)
Raggi ⁴¹	2001	USA	676	52	51	3	CACS	CHD†	4.4	0.71	0.84	—
Wong ⁴²	2009	USA	2303	56	62	4	CACS categories 0 to 9, 10 to 99, 100 to 399, and ≥400	CVD†	1.8	0.76	0.85	—

The baseline prediction model used in each of the studies is described in supplementary table 1 (available online only).

*Thresholds for intermediate risk were an absolute predicted 10 year risk between 10% and 20%,³⁷ a 5 year predicted risk between 10% and 20%³⁸ or 3–10%.^{10 40}

†Non-fatal and fatal events.

CACS, coronary artery calcification score; CHD, coronary heart disease; CVD, cardiovascular disease; FU, follow-up; NRI, net reclassification improvement.

predictive research.^{54–57} Also, FMD measurements need to be further standardised and technical aspects, such as occlusion time and cuff location, should be carefully considered given their impact on the results of an FMD measurement.⁵⁸

In contrast, carotid ultrasound measurements of CIMT and plaque have been shown to improve risk prediction in a number of studies although the extent of this added value varies across studies which may, at least partly, be due to differences in study populations and ultrasound protocols used. We therefore do not believe that a large additional single cohort study is needed but rather a meta-analysis based on individual participant (IPD) data pooled from the existing cohort studies aimed at more precisely quantifying the additional predictive value of carotid ultrasound measurements in the correct domain.⁵⁹ If such IPD meta-analysis is confirmative, the next step is to quantify the impact and costs of carotid ultrasound measurements added to conventional prediction model on patient care and clinical outcomes.

The evidence for CAC consistently shows that it improves conventional risk prediction, and the methods of measuring CAC were largely similar across studies. Accordingly, for CAC, the next phase also seems to be a more comprehensive quantification of whether the use of a traditional prediction model extended with CAC is cost-effective, improves clinical decision making and ultimately improves patient outcome.⁵⁵ For both carotid ultrasound and CAC, results from studies quantifying the population benefits and costs are needed before an evidence based decision about its widespread application can be made.^{55 60}

Limitations

Our systematic search was comprehensive and carefully conducted but we restricted our search strategy to PubMed and we therefore may have missed relevant studies that are not accessible in PubMed. In addition, papers may have been missed while reviewing titles and abstract. However, our search results were reviewed in duplicate and we crosschecked the references of the papers dealing with this topic.

In contrast with randomised, therapeutic, diagnostic and even to some extent aetiological studies, there are no formal tools available to critically appraise the applied methods and biases in prediction modelling studies.^{16–20} Hence we could not formally appraise the included studies as such. Nevertheless, we have critically appraised the quality of the included papers and found good reporting of the predefined methodological criteria except for the reporting of the presence of missing values and on the reasons for lost to follow-up, both of which could lead to some selection bias in the respective studies.

Also, the lack of studies reporting a small added value of CAC may indicate that the added predictive value is indeed relatively large compared with FMD, CIMT and carotid plaque. However, it may also indicate that studies that have found smaller additional predictive values have not been published.

In addition, it may be that some of the included studies used suboptimal methods to evaluate the added predictive value of a marker of atherosclerosis and, for example, overfitting or optimism of the predictive models may have occurred.⁵⁷ However, as the main aim was to review the papers that quantified the added predictive value of imaging markers within the same study population and not across studies, this potential for bias and overfitting was the same for the basic and extended prediction models. As such, the difference in predictive accuracy (eg, the c-index or NRIs) between the basic and extended prediction model is likely to be unaffected as both models are derived in the same way.

Finally, while the NRI is increasingly being used, its results depend on the actual risk thresholds used.^{15 61 62} Therefore, comparing NRI results across studies is meaningless unless the risk thresholds are equal. Yet risk thresholds in CVD prevention are fairly consistent as high risk is considered as a 10 year absolute risk of at least 20% to develop a hard CVD event, and low risk from intermediate risk ranges between 6% and 10%.^{4 51 63 64}

CONCLUSION

Published evidence on the added value of atherosclerosis imaging varies across markers, with limited evidence for FMD and considerable evidence for CIMT, carotid plaque and CAC. The added predictive value of additional screening may be primarily found in asymptomatic individuals at intermediate cardiovascular risk. Additional research is needed to quantify the impact and cost effectiveness of imaging markers for subclinical atherosclerosis in addition to the classical markers on patient management and clinical outcomes.

Competing interests MLB has received grants from profit and non-profit organisations for carotid intima-media thickness (CIMT) studies and for consultancy regarding CIMT research. He runs the Vascular Imaging Centre Utrecht, a core laboratory for CIMT measurements in national and international observational and intervention studies. KGMM receives funding from the Netherlands Organisation for Scientific Research (project 9120.8004 and 918.10.615).

Contributors SAEP and HMR contributed to study selection, data extraction, and the writing and editing of the manuscript. MLB and KGMM contributed to drafting and revising the article. All authors had important intellectual content and approved the final version of the manuscript.

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Supplementary table 1: Description of variables in baseline prediction models used across studies

First author	a g e	s e x	r a c e	b m i	h d l c	l d l c	t c	t r i	s b p	d b p	b p	h r	s m o k	d m	l l - 6	h c l	h p t	l v h	c v d	st a t	a f †	b p m	
Flow-mediated dilation																							
Yeboah[19]	x	x				x		x	x			x	x						x	x			
Yeboah[11]	x	x			x	x		x	x			x	x	x							x		x
Carotid intima-media thickness																							
Anderson[20]*	x	x			x		x		x	x			x	x									
Cao[21]	x	x	x	x	x	x	x		x	x			x	x									
Chambless[22]					x		x		x				x	x								x	
Chambless[23]									x				x	x				x	x			x	
Elias-Smale[29]**	x	x			x		x		x	x			x	x								x	
Folsom[25]	x	x	x		x		x				x		x	x							x		
Lorenz[28]	x	x			x	x			x	x			x	x									
Mathiesen[26]	x				x		x		x				x	x					x			x	
Nambi[9]	x	x			x		x		x				x	x								x	
Polak[30]**	x	x			x		x		x	x			x	x									
Price[27]	x	x			x		x		x				x	x									
del Sol[24]	x	x			x		x		x	x			x	x					x				
Carotid plaque																							
Cao[21]	x	x	x	x	x	x	x		x	x			x	x									
Mathiesen[26]	x				x		x		x				x	x					x			x	
Nambi[9]	x	x			x		x		x				x	x								x	
Prati[31]**	x	x			x		x		x	x			x	x									
Stork[32]	x														x								
Xie[33]	x	x			x		x						x	x				x					
Coronary artery calcification score																							
Detrano[34]	x	x	x		x		x		x	x			x	x							x		x
Elias-Smale[35]**	x	x			x		x		x	x			x	x									
Erbel[36]*	x	x			x		x		x	x			x	x									
Folsom[25]	x	x	x		x		x				x		x	x							x		
Greenland[37]*	x	x			x		x		x	x			x	x									
Mohlenkamp[38]	x	x			x		x															x	
Polonsky[10]	x	x	x		x		x		x	x			x	x									
Raggi[39]	x	x											x	x		x	x						
Wong[40]*	x	x			x		x		x	x			x	x									

* the original Framingham risk score was used as baseline model, ** a recalibrated version of the Framingham risk score was used as baseline model, † this risk factor was only included in the prediction model with stroke as outcome

Abbreviations: bmi, body mass index; hdlc, high-density lipoprotein cholesterol; ldlc, low-density lipoprotein cholesterol; tc, total cholesterol; tri, triglycerides; sbp, systolic blood pressure; dbp, diastolic blood pressure; bp, blood pressure; hr, heart rhythm; smok, smoking; dm, diabetes mellitus; il-6,

interleukin-6; hcl, hypercholesterolemia; hpt, hypertension; lvh, left ventricle hypertrophy; cvd, history of cardiovascular disease; stat, use of statins; af, arterial fibrillation; bpm, use of blood pressure lowering medication

Supplementary table 2: Methodological quality appraisal items scored on each included study.

Study Feature	Study participants				Attrition				Prognostic variable			Outcome		Analysis	
	Relevant domain	Participant selection	In- and exclusion criteria	Baseline characteristics	Participation rate	Response rate	Data collection drop-outs	Reasons loss to follow-up	Definition marker	Measurement method	Missing values	Definition outcome	Outcome ascertainment	Missing values	Presentation
Flow-mediated dilation															
Yeboah[19]	x	x	x	x	x	x	-	-	x	x	-	x	x	-	x
Yeboah[11]	x	x	x	x	x	x	-	-	x	x	-	x	x	-	x
Carotid intima-media thickness															
Anderson[20]	x	x	x	x	-	x	-	-	x	x	-	x	x	-	x
Cao[21]	x	x	x	x	x	-	-	x	x	x	x	x	x	x	x
Chambless[22]	x	x	x	x	x	x	-	-	x	x	x	x	x	x	x
Chambless[23]	x	x	x	x	x	x	-	-	x	x	-	x	x	x	x
Elias-Smale[29]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Folsom[25]	x	x	x	x	x	x	-	-	x	x	x	x	x	x	x
Lorenz[28]	x	x	x	x	x	-	-	-	x	x	-	x	x	-	x
Mathiesen[26]	x	x	x	x	x	x	-	-	x	x	-	x	x	-	x
Nambi[9]	x	x	x	x	x	x	-	-	x	x	x	x	x	x	x
Polak[30]	x	x	x	x	x	x	-	-	x	x	x	x	x	x	x
Price[27]	x	x	x	x	x	x	x	-	x	x	-	x	x	-	x
del Sol[24]	x	x	x	x	x	x	-	-	x	x	x	x	x	-	x
Carotid plaque															
Cao[21]	x	x	x	x	x	-	-	x	x	x	x	x	x	-	x
Mathiesen[26]	x	x	x	x	x	x	-	-	x	x	-	x	x	-	x
Nambi[9]	x	x	x	x	x	x	-	-	x	x	x	x	x	x	x
Prati[31]	x	x	x	x	x	x	-	-	x	x	-	x	x	-	x
Stork[32]	x	x	x	x	x	x	x	x	x	x	-	x	x	-	x
Xie[33]	x	x	x	x	x	x	-	-	x	x	x	x	x	x	x
Coronary artery calcification score															
Detrano[34]	x	x	x	x	x	x	-	-	x	x	-	x	x	x	x
Elias-Smale[35]	x	x	x	x	x	x	-	-	x	x	x	x	x	x	x
Erbel[36]	x	x	x	x	x	x	-	-	x	x	x	x	x	x	x
Folsom[25]	x	x	x	x	x	x	-	-	x	x	x	x	x	x	x
Greenland[37]	x	x	x	x	x	x	-	-	x	x	-	x	x	-	x
Mohlenkamp[38]	x	x	x	x	x	x	-	-	x	x	x	x	x	x	x
Polonsky[10]	x	x	x	x	x	x	-	-	x	x	-	x	x	-	x
Raggi[39]	x	x	x	x	x	x	-	-	x	x	-	x	x	-	x
Wong[40]	x	x	x	x	x	x	-	-	x	x	-	x	x	-	x

x: issue has been reported; -: issue has not been reported or addressed. This table indicates whether each item was indeed addressed in each individual study, but does not easily allow to judge whether a bias was indeed present or absent.