Comparative performance of subclinical atherosclerosis tests in predicting coronary heart disease in asymptomatic individuals

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Received 18 April 2007; revised 13 September 2007; accepted 26 September 2007; online publish-ahead-of-print 29 October 2007

KEYWORDS
Primary prevention;
Intima–media thickness;
Plaque;
Atherosclerosis;
Arterial stiffness;
Coronary calcium;
Cardiovascular risk

The prognostic performance of subclinical atherosclerosis in predicting coronary heart disease (CHD) needs to be clarified because of the existence of many non-invasive tests available for its detection in the clinical setting: ultrasound measurement of carotid intima–media thickness (IMT) and plaque, cardiac computed tomography assessment of coronary artery calcium, Doppler stethoscope measurement of ankle–arm index pressure (AAI), and mechanographic or Doppler determination of aortic pulse wave velocity (PWV). Data analysis of the main prospective studies in asymptomatic populations allows the establishment of a dose–response relationship between subclinical atherosclerosis burden and cumulative incidence of future CHD event (absolute risk). Negative subclinical atherosclerosis testing conveys a low 10-year CHD risk inferior to 10% whatever the test considered, i.e. IMT less than the 1st tertile or 1st quintile, AAI ≤ 0.90, PWV less than the first tertile, no discernible carotid plaque, or zero coronary calcium score. Positive testing for IMT (>95th percentile or 5th quintile), AAI (<0.90), or PWV (>3rd tertile) conveys a moderately high 10-year CHD risk between 10 and 20%. Positive testing for carotid plaque (focal protrusion >1.5 mm or mineralization) or coronary calcium (total score >300 or 400 units) conveys a high 10-year CHD risk superior to 20%. Therefore, positive subclinical atherosclerosis measurement seems to have its place in the context of existing prediction models, namely for intermediate risk classification. It also remains to be established whether individuals with negative subclinical atherosclerosis may be considered at low CHD risk and receive conservative management.

Introduction
Better identification of asymptomatic individuals at high risk of future coronary heart disease (CHD) and who should therefore receive aggressive risk reduction therapy is an important challenge for primary prevention of cardiovascular disease.1 Despite their aetiological importance in atherosclerosis, cardiovascular risk factors have a poor performance in predicting asymptomatic subjects who will or will not develop CHD.2 A large overlap exists in the distributions of both the major risk factors, serum cholesterol and blood pressure, in men who died of CHD and in those who did not.2 Moreover, more than half of subjects with CHD have no major risk factor, or only one.3 Conversely, the well-established high prognostic performance of clinically overt arterial disease4,5 has supported the idea of extrapolating the prognostic performance of clinical arterial disease to subclinical disease.1 The observation that arterial disease does not begin with the first clinical event but develops long before without symptoms has motivated much biotechnological medical research for the detection of subclinical disease4–8. The more commonly used subclinical vascular markers in the clinical setting are carotid intima–media thickness (IMT) and plaque measured by ultrasound, coronary artery calcium detected by cardiac computed tomography (CT), ankle–arm index pressure (AAI) measured by distal pressure Doppler measurement, and aortic pulse wave velocity (PWV) measured from carotid and femoral pressure wave recordings with a Doppler or mechanographic device.1 For individuals at intermediate risk, e.g. 10–20% 10-year Framingham risk of fatal and non-fatal CHD4 or 3–5% European SCORE9 risk of fatal cardiovascular disease, clinicians may consider testing for subclinical atherosclerosis and, in those with a positive test, aggressive risk reduction intervention may be appropriate.8–11 Nevertheless, the implementation of subclinical atherosclerosis testing in the risk management of patients is dependent on a better knowledge of the comparative prognostic performance of various tests of atherosclerosis currently available.

In this report, the prognostic performance of subclinical atherosclerosis testing is discussed on the basis of crude CHD incidence (absolute risk) associated with positive and negative subclinical atherosclerosis testing.12
Methods

Studies and subjects

Using MEDLINE and review articles, we identified published studies in which subclinical atherosclerosis was detected with the most important non-invasive tests currently being used, and in which patients were followed prospectively to determine the occurrence of CHD events (Table 1): Atherosclerosis Risk in Communities (ARIC),

Cardiovascular Health Study (CHS),

Kuopio Ischemic Heart Disease (KIHD),

South Bay Heart Watch study (SBHW),

St Francis Heart study (SFHS),

and the Rotterdam Study (ROT).

These studies fulfilled the main quality criteria defined by the group Meta-analysis Of Observational Studies in Epidemiology (MOOSE) and listed in the statement for Strengthening the Reporting of Observational studies in Epidemiology (STROBE): (i) background, objective, and key elements of study design were clearly defined; (ii) eligibility criteria, participant selection methods without bias, and baseline characteristics of participants were properly described; (iii) precise definition and report of the number of CHD outcomes were provided. Lastly, study participants were free of symptoms and history of clinical cardiovascular disease at inclusion. Age and gender characteristics of the subjects in the included studies are shown in Table 2.

Data analysis

Published aggregate data of the studies considered for this review allowed calculation of CHD incidence according to the presence or absence of subclinical atherosclerosis at baseline. The CHD incidence rate was calculated as the number of events divided by study persons-time. The cumulative 10-year CHD risk was determined by using an exponential survival model and assuming the CHD rate to be constant, by means of the formula: 10-year CHD risk = 1 - EXP(-10*), being the annual CHD rate deducted from each study. Data are descriptive without specific statistical analysis, with the exception of the relationship between subclinical atherosclerosis determination and CHD risk that was obtained by curve model analysis after having coded the results of subclinical atherosclerosis testing (Figure 1).

Results

Coronary risk of positive subclinical atherosclerosis testing

Carotid IMT and plaque (Table 2)

In middle-aged subjects of the ARIC study, ultrasound evidence of markedly increased carotid overall mean IMT (average of IMT measures in common carotid, bifurcation, and internal carotid on both sides above the 95th percentile) was associated with 14 and 11% 10-year CHD risk in men and women, respectively. In older subjects of both sexes of the CHS study, a marked increase in the maximal common carotid IMT in the 5th quintile was associated with 15% 10-year CHD risk. In middle-aged men of the KIHD study, ultrasound detection of focal intrusive plaque or mineralization in extracranial carotid arteries was associated with a 10-year risk of myocardial infarction/CHD as compared with categorization according to a single measure of IMT or plaque.

AAI and PWV (Table 2)

In elderly subjects of the CHS study, decreased AAI below 0.9 (that is evidence of asymptomatic peripheral arterial disease) was associated with a 15% 10-year CHD risk. In elderly subjects of the Rotterdam study, a marked increase in aortic PWV in the 3rd tertile adjusted for age and gender (that reflects systemic large arteries stiffening) was associated with a 13% 10-year CHD risk.

Coronary risk of negative subclinical atherosclerosis testing

Carotid IMT and plaque (Table 2)

In middle-aged subjects of the ARIC study, the lowest values of carotid overall mean IMT (in the 1st tertile) were associated with a 10-year CHD risk of 3% in men and 1% in women. In older subjects of both sexes of the CHS study, the lowest values of maximal common carotid IMT (in the 1st quintile) were associated with a 4% 10-year CHD risk. In middle-aged men of the KIHD study, absence of any plaque and wall thickening in extracranial carotid arteries was associated with a 8% 10-year CHD risk.

Table 1 Characteristics of prospective studies in asymptomatic subjects undergoing subclinical atherosclerosis testing at the onset of follow-up

<table>
<thead>
<tr>
<th>Study</th>
<th>Test</th>
<th>Follow-up duration (years)</th>
<th>CHD end-point</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Carotid IMT</td>
<td>5.2</td>
<td>Myocardial infarction/CHD death/revascularization</td>
</tr>
<tr>
<td>CHS&lt;sup&gt;14,23&lt;/sup&gt;</td>
<td>Carotid IMT</td>
<td>6.2</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>KIHD&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Carotid plaque</td>
<td>1</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>SBHW&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Coronary calcium</td>
<td>7</td>
<td>Myocardial infarction/CHD death</td>
</tr>
<tr>
<td>SFHS&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Coronary calcium</td>
<td>4.3</td>
<td>Myocardial infarction/CHD death/revascularization</td>
</tr>
<tr>
<td>ROT&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Aortic PWV</td>
<td>4.1</td>
<td>Myocardial infarction/CHD death/revascularization</td>
</tr>
</tbody>
</table>

ARIC, Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; KIHD, Kuopio Ischemic Heart Disease; SBHW, South Bay Heart Watch study; SFHS, St Francis Heart Study; ROT, Rotterdam study. CHD, coronary heart disease; IMT, intima–media thickness; PWV, pulse wave velocity. Superscripts are references.
In elderly subjects of the CHS study, normal AAI (C0.90) was associated with an 8% 10-year CHD risk and, in elderly subjects of the Rotterdam study, the lowest values of PWV (in the 1st tertile) were associated with a 4% 10-year CHD risk.

Coronary calcium score (Table 2)
In the middle-aged predominantly male population of the SBHW study, the absence of coronary calcium deposit evidenced by a zero calcium score at cardiac CT was associated with a 6% 10-year CHD risk. In older men and women of the SFHS study, evidence of a zero calcium score was associated with a 1% 10-year CHD risk.

Dose–response curve between subclinical atherosclerosis and CHD risk
A dose–response curve relating the absence and presence of subclinical atherosclerosis with 10-year CHD risk was obtained by pooling the results of studies with a similar CHD end-point (e.g. combined myocardial infarction or CHD death, as well as combined myocardial infarction, CHD death, or revascularization) (Figure 1). Negative subclinical atherosclerosis testing, whatever the test used, was associated with a <10% ten-year CHD risk (Figure 1). Conversely, positive subclinical atherosclerosis testing was associated with a 10-year CHD risk of between 10 and 30% (Figure 1). Moreover, CHD risk depended on the type of test used, with a maximum risk of 30% associated with cardiac CT-assessed massive coronary calcium deposit (Figure 1).

The graded relationship between absolute CHD risk and atherosclerosis burden provides evidence that subclinical arterial disease is a true risk marker of a future CHD event in asymptomatic individuals. However, such prognostic information is limited in several ways: data are lacking in younger individuals who should benefit most from ultrasound assessment of carotid arteries for early detection of high CHD risk; also, data on carotid plaque and coronary calcium were obtained in exclusively or predominantly male populations and may not be extrapolated as such to women.

Discussion
Positive testing for subclinical atherosclerosis is associated with a moderately high to high CHD risk, but the different types of subclinical atherosclerosis tests have a different prognostic performance (Figure 1). Positive testing for IMT,
A decision-analytic approach taking potential benefit and harm into account, possibly in a randomized trial. Such a trial does not exist to our knowledge, and the decision of whether to carry out subclinical atherosclerosis testing is therefore discussed empirically and selectively by the physician with a view to improving and supplementing (but not replacing) the classical risk prediction assessment, but not to making a diagnosis of cardiovascular disease. In subjects at low traditional risk, positive subclinical atherosclerosis testing does not contribute to CHD risk management because their treatment on the basis of this test has no support at present, except perhaps in those in the upper range of the low risk category (e.g. 6–9% Framingham risk) wherein risk factor reduction might be worth intensifying to intermediate target levels (e.g. for low-density lipoprotein cholesterol) but not to the high risk target level. Also, subclinical atherosclerosis detection does not change the clinical management of subjects at high traditional risk because they should have risk factors treated intensively no matter what such detection reveals. Finally, in subjects with intermediate or uncertain traditional risk, positive subclinical atherosclerosis testing may reasonably allow their re-classification into a higher category of risk and justify treating them more aggressively. In contrast, it is uncertain whether negative subclinical atherosclerosis testing may allow the re-classification of these subjects into a lower category of risk.

### Study limitations

First, the calculation of cumulative CHD incidence over a 10-year period from studies with a shorter follow-up duration, especially the 1-year follow-up KIHD study (Table 1), was based on the assumption of a constant CHD rate over 10 years. It is likely that this assumption underestimated CHD risk because of the strong influence of age in prediction models. Secondly, the differences in outcomes across the studies considered for this review constitute a limitation in comparing CHD incidences between studies. Thirdly, the predictions from models using subclinical vascular markers, possibly according to cut-offs, have not yet been validated. Fourthly, individual patient data of the studies were not analysed; only aggregate data in groups of subjects were extracted to derive cumulative CHD incidences according to the reported test result. Also, the Framingham functions were not used for risk assessments; only the 10-year

### Table 3 Criteria for choosing subclinical atherosclerosis test

<table>
<thead>
<tr>
<th>Test criteria</th>
<th>Carotid IMT</th>
<th>Ankle–arm index</th>
<th>Aortic PWV</th>
<th>Carotid plaque</th>
<th>Coronary calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictive value</td>
<td>Fair</td>
<td>Fair</td>
<td>Fair</td>
<td>Excellent</td>
<td>Excellent</td>
</tr>
<tr>
<td>Simplicity</td>
<td>Good</td>
<td>Excellent</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>Excellent</td>
<td>Fair</td>
<td>Excellent</td>
<td>Fair</td>
<td>Fair</td>
</tr>
<tr>
<td>Safety</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Good</td>
</tr>
<tr>
<td>Low cost</td>
<td>Good</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Poor</td>
</tr>
</tbody>
</table>

For acronyms, see Table 1.
Framingham ATP III cut-offs\(^4\) of low (<10%), intermediate (10–20%), and high (>20%) risk of fatal and non-fatal CHD were used for interpreting the clinical relevance of the cumulative CHD incidence rate associated with subclinical markers (Figure 1). Lastly, no validation studies have yet shown whether predicted risks generalize to truly new, external data; also, none of the cut-offs recommended in Table 1 have been validated in new patients.

In conclusion, further studies are needed to define the exact place of subclinical atherosclerosis testing in the context of existing risk factor-based models for CHD prediction and for choosing and standardizing the optimal test(s) required for accurate assessment of atherosclerosis burden. In addition to prognostic performance, other criteria for the choice of subclinical atherosclerosis test, such as simplicity, accuracy, safety, and low cost, need to be taken into account (Table 3). However, it is noteworthy that any subclinical atherosclerosis test currently used does not correctly fulfill all the required criteria for optimal testing (Table 3).

**Conflict of interest:** none declared.

**References**


