Performance of Subclinical Arterial Disease Detection as a Screening Test for Coronary Heart Disease

Alain Simon, Gilles Chironi, Jaime Levenson

Abstract—Traditional risk factors are poor screening tests for coronary heart disease, whereas clinical arterial disease represents its strongest predictor. This raises the question whether subclinical arterial disease may also predict coronary disease. Using published data of prospective studies of subclinical arterial disease, we calculated the incidence of coronary event associated with the absence or presence of atherosclerosis as defined by dichotomous characterization of the following markers: low or high intima-media thickness or the absence or presence of plaque, assessed by carotid ultrasound; zero or high total coronary artery calcium score assessed by computed tomography; normal or decreased ankle-arm index pressure assessed by Doppler stethoscope; and low or high aortic pulse wave velocity assessed by mecanography. A dose–response relationship was found between the absence and presence of atherosclerosis and coronary event incidence. Yearly incidence was <1% in the absence of atherosclerosis regardless of the marker used. Coronary event incidence was >1% in the presence of atherosclerosis and increased in a gradual way, depending on the marker tested, to reach 3% maximum with massive coronary calcifications. The relation between clinically overt arterial disease, such as angina, transient ischemic attack, stroke, or myocardial infarct, and yearly incidence of subsequent events reported in the literature prolonged the dose–response curve of subclinical disease. Therefore, detection of arterial disease, not only clinically overt but also subclinical asymptomatic, is a worthwhile screening test for future coronary event. (Hypertension. 2006;48:392-396.)

Key Words: risk factors □ coronary heart disease □ intima-media thickness □ coronary calcium □ plaque □ arterial stiffness □ prevention

Despite their etiologic importance in atherosclerosis, traditional cardiovascular risk factors are not accurate in predicting subjects who will and will not develop coronary heart disease (CHD). Approximately 80% overlap exists in distributions of serum cholesterol and blood pressure in men who died of CHD and in those who did not. Also, more than half of subjects with CHD have not any, or only 1, major risk factor. As a result, CHD incidence associated with conventional risk factors in asymptomatic people is <1% per year except in diabetic men. Conversely, the existence of clinically overt arterial disease is a very potent predictor of cardiovascular events. One analysis of studies completed before 1980, and following patients after myocardial infarct in the absence of modern therapy, has shown that the incidence rate of cardiovascular death after a first myocardial infarction approximated 5% per year. However, arterial disease does not begin with the first clinical event but develops long before without symptom, supporting the idea to extrapolate the high prognostic performance of clinical arterial disease to subclinical disease and motivating much biotechnological medical research. Because the potential performance of subclinical atherosclerosis for predicting CHD risk for asymptomatic persons remains a debated question, we tried to provide an original contribution to this debate by calculating the annual incidence rate of CHD events in relation to the presence or absence of subclinical arterial disease from the analysis of published prospective population-based studies of subclinical atherosclerosis.

Methods

Subjects
Our analysis was deliberately restricted to prospective population-based studies in which subclinical atherosclerosis was appropriately detected at the onset of follow-up: Atherosclerosis Risk in Communities, Cardiovascular Health Study, Kuopio Ischemic Heart Disease, South Bay Heart Watch Study, St Francis Heart studies, and Rotterdam Study. We used published data on a number of coronary events occurring during the follow-up in subjects with and without subclinical atherosclerosis, at inclusion in the study. Age range and sex distribution are shown in Table 1. Subjects at inclusion were symptom free and without history of clinical cardiovascular disease. All of the studies were approved by an institutional review committee, and the subjects gave informed consent.
Atherosclerosis

The type of atherosclerosis markers by studies is shown in Table 1. Carotid intima–media thickness (IMT) was measured by ultrasound and defined either as the average of measures at 6 sites (mean overall IMT) in the far wall for 1-cm lengths of the carotid bifurcation and the internal carotid and common carotid, right and left, or as the average of the maximal IMT (maximal IMT) in the near and far wall of right and left common carotid segments. Carotid plaque was detected by ultrasound interrogation of both extracranial carotid arteries and defined as present when a distinct area could be identified either with mineralization or with focal profusion into the lumen. Total coronary calcium score was calculated by computed tomography using either with mineralization or with focal profusion into the lumen. Total coronary calcium score was calculated by computed tomography using either with mineralization or with focal profusion into the lumen. Total coronary calcium score was calculated by computed tomography using either with mineralization or with focal profusion into the lumen.

Maximal CCA

Carotid plaque

Present

Absence

Coronary artery calcium

Score 301

Score 0

Score 400

Score 0

Ankle arm index

<0.90

≥0.90

PWV

>14.6, 14.2 m s⁻¹ (M, W)

<12.3, 11.9 m s⁻¹ (M, W)

Data Analysis

The data are descriptive without specific statistical analysis, with the exception of the relationship between atherosclerosis burden and incidence of coronary event that was obtained by logarithmic model analysis after having coded the results of the testing of subclinical atherosclerosis and the clinical forms of arterial disease (Figure).

Results

Table 1 shows the proportion of patients developing a CHD event during the time of the follow-up and the yearly CHD incidence according to the presence or the absence of atherosclerosis. Values of carotid IMT above the 95th percentile, or within the 5th tertile, were associated with 1.2% to 1.6% yearly incidence of CHD depending on age, sex, and type of IMT measure, whereas lowest carotid IMT values were associated with 2.8% yearly CHD incidence per year, whereas absence of coronary calcium was associated with 0.5%. It is noteworthy that coronary event incidence associated with values of carotid IMT above the 95th percentile was 25% greater in men than in women, and event incidence associated with lowest IMT values (1st tertile) was 3 times greater in men than in women. The presence of carotid plaque was associated with 2.8% yearly CHD incidence per year, whereas normal carotid wall was associated with CHD incidence <1%. Coronary calcium score >300 or 400 U was associated with 2.2% and 3.3% yearly incidence of CHD, whereas absence of coronary calcium was associated with

CHD End Point and Incidence

Subjects were followed prospectively to determine the incidence of CHD event over a period of time ranging from 1 to 7 years (Table 1). CHD end point included myocardial infarction (MI) alone, or combined MI or CHD death, or revascularization procedures. The yearly incidence of CHD was calculated as the proportion of subjects developing the CHD end point during the follow-up divided by the average follow-up duration.
CHD incidence ≤0.6%. Decreased ankle arm index <0.90 was associated with 1.6% yearly incidence of CHD, whereas value >0.90 was associated with <1% CHD incidence. Age- and gender-adjusted 3rd tertile values of PWV were associated with 1.4% yearly incidence of CHD, whereas 1st tertiles values were associated with 0.4% CHD incidence. The Figure shows that the positive dose–response relationship existing between yearly incidence of CHD and the absence and presence of subclinical atherosclerosis defined by dichotomous characterization of each tested marker.

**Discussion**

Yearly CHD incidence is the more basic and raw information characterizing coronary risk and allowing the calculation of 10-year CHD risk. Using published data of prospective studies of subclinical arthrosclerosis in asymptomatic population-based subjects of various age and sex, we, therefore, calculated yearly CHD incidence by absence or presence of atherosclerosis. The latter was assessed noninvasively by dichotomous characterization of following arterial markers: low or high carotid IMT, absence or presence of carotid plaque, 0 or high total coronary calcium score, normal or decreased ankle arm index pressure, and low or high aortic PWV. This approach is simpler and more clinically relevant for estimating the prognostic performance of subclinical atherosclerosis detection than the classical interpretation of the odds ratio that is not exempt from limitations in gauging the performance of a prognostic marker.17

Evidence of subclinical atherosclerosis was associated with CHD incidence value ranging from 1.2% to 3.3% per year according to age, gender, and type of marker, thereby conveying a 10-year CHD risk from 12% to 33% that corresponds with moderate-to-high risk condition.4 Such CHD incidence is notably greater than the 1% per year CHD incidence associated with conventional risk factors, except diabetes, in asymptomatic people (Table 2).1,3 A possible reason is that the prediction of event is better with a marker of the consequence of the disease than with a marker of etiologic nature as a conventional risk factor.1 These findings constitute strong arguments for considering that the

**TABLE 2. CHD Incidence by Presence of Traditional Major Risk Factors in Asymptomatic Persons**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Sex, Age, y</th>
<th>Yearly CHD Incidence, %</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Both sexes, 58</td>
<td>0.89</td>
<td>Placebo groups of randomized trials20</td>
</tr>
<tr>
<td>LDL-C &gt;1.60 g/L</td>
<td>Men, 45 to 65</td>
<td>0.90</td>
<td>ARIC3</td>
</tr>
<tr>
<td></td>
<td>Women, 45 to 65</td>
<td>0.50</td>
<td>ARIC3</td>
</tr>
<tr>
<td>Smoking</td>
<td>Men, 45 to 65</td>
<td>1.0</td>
<td>ARIC3</td>
</tr>
<tr>
<td></td>
<td>Women, 45 to 65</td>
<td>0.50</td>
<td>ARIC3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Men, 45 to 65</td>
<td>1.40</td>
<td>ARIC3</td>
</tr>
<tr>
<td></td>
<td>Women, 45 to 65</td>
<td>0.90</td>
<td>ARIC3</td>
</tr>
</tbody>
</table>

ARIC indicates Atherosclerosis Risk in Communities; LDL-C, low-density lipoprotein cholesterol. Superscript number indicates bibliographic reference.
presence of subclinical atherosclerosis in asymptomatic subjects with moderate cardiovascular risk indicates incremental risk,3,9 provided that the criteria defining subclinical atherosclerosis in the analyzed studies are used. This means that carotid IMT must be above the 95th percentile or within the 5th quintile, carotid plaque must be present, total coronary calcium score must exceed 300 or 400 U, ankle arm index pressure must be decreased <0.90, or high aortic PWV must be within the 3rd tertile for age and sex. By contrast, CHD incidence associated with subclinical atherosclerosis was far below the 5% per year incidence of cardiovascular death reported after MI,5 demonstrating that subclinical disease is a less potent predictor of subsequent event than clinically overt arterial disease. Lastly, gender difference can play an important role in the predictive capacity of subclinical atherosclerosis, as shown by the Atherosclerosis Risk in Communities Study.3 It has analyzed men and women separately, thereby allowing observation that the highest IMT values are associated with greater incidence of coronary events in men than in women. This finding agrees with the gender difference, reported by the same study,3 in the incidence of coronary events associated with traditional risk factors (increased low-density lipoprotein cholesterol, smoking, and diabetes) that was 1.5 to 2 times greater in men than in women (Table 2).

We also found that absence of atherosclerosis was associated with 0.1% to 0.8% per year incidence of subsequent CHD, that is to say a 10-year CHD risk clearly <10% that unquestionably represents a low-risk status.4 This finding is not sufficiently emphasized in the literature and supports the idea that a negative subclinical atherosclerosis test may identify low-risk individuals who do not need further cardiac medication. Obviously, this attitude is subordinated to the strict use of the criteria defining absence of subclinical atherosclerosis in the analyzed studies (ie, carotid IMT value within the 1st quintile or tertile, absence of carotid plaque and normal wall thickness, total calcium score equal to 0, ankle arm index ≥0.90, or PWV value within the 1st tertile). Although its implementation should be a source of health cost savings, the idea that absence of subclinical atherosclerosis is an equivalent of low CHD risk is not yet accepted in current guidelines,4,9,18 and further validation studies are needed.

Finally, we found a dose–response relationship between the absence and presence of subclinical atherosclerosis and CHD incidence. Yearly incidence was <1% in the absence of atherosclerosis, whatever marker was used, and the lowest incidence of 0.1% was attained with absence of coronary calcifications. By contrast, CHD incidence was >1% in the presence of atherosclerosis and increased in a gradual way, depending on the marker tested, until it reached 3% maximum with massive coronary calcifications. Interestingly, the relation of clinically overt arterial disease, such as angina, transient ischemic attack, stroke, and MI, with the incidence of subsequent cardiovascular death reported in the literature,5,19,20 prolonged perfectly the dose–response curve of subclinical disease (Figure). This continuous relation of CHD incidence with subclinical and clinically overt arterial disease is of logarithmic type (Figure) and establishes and quantifies the strength of arterial disease as a risk marker for a CHD event, whatever the stage of disease development.19

Study Limitations
Several limitations related to heterogeneity of coronary end points and tests of subclinical atherosclerosis and insufficient data in younger individuals deserved to be pointed out. First, the CHD end point was not the same across the studies, and studies that have analyzed only myocardial infarct outcome may have underestimated coronary event incidence as compared with studies having analyzed combined myocardial infarct, coronary death, and revascularization procedures. Also, there is a great heterogeneity across studies in noninvasive tests for detecting the presence or absence of subclinical atherosclerosis. The choice of the optimal test is not supported by the present data nor is the important question of whether the combination of several tests of subclinical atherosclerosis may provide incremental prognostic information as compared with the use of a single test. Lastly, no data exist in subjects <40 to 45 years of age who are more often carriers of intermediate cardiovascular risk than of high CHD risk and might, therefore, benefit particularly from the testing of subclinical atherosclerosis.

In conclusion, identifying asymptomatic individuals with unequivocal subclinical arterial disease may be considered as the best current screening test for predicting subsequent CHD events and offering them aggressive risk reduction therapy. Further studies are needed, however, for defining the exact place of subclinical atherosclerosis testing in patient management before or after traditional risk factors assessment and for choosing and standardizing the optimal test(s) required for accurately assessing atherosclerosis burden. On the other hand, it remains to be established more definitely whether individuals without subclinical atherosclerosis may be considered at low risk and whether the intensity of their risk reduction therapy may be reduced accordingly.

Disclosures
None.

References
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