The Value of Carotid Intima-Media Thickness for Predicting Cardiovascular Risk

Alain Simon, Jean-Louis Megnien, Gilles Chironi

Abstract—We reviewed prospective epidemiological data in the general population, mostly middle-aged to older persons, to determine the association of carotid intima-media thickness (CIMT) (assessed by B-mode ultrasonography) with cardiovascular risk. Reported risks were expressed as absolute (event risk per persons-years in subjects with a high CIMT) and relative (hazard ratio of high vs low CIMT). They were hardly comparable as the result of differences between the analyzed studies, including the site and procedure of CIMT measurement, the report of adjusted or unadjusted models, and the arbitrary cutoff point to evaluate the CIMT ability to predict risk. Despite these heterogeneities, the following four main conclusions emerged: (1) CIMT was an independent but relatively modest (as judged by absolute risk) predictor of coronary heart disease (CHD); (2) CIMT was an independent predictor for stroke, slightly better than for CHD as judged by the relative risks of both events; (3) CIMT added little to the CHD prediction by risk factors, as judged by c statistic and receiver operating characteristic curve analysis (however, appropriate data for stroke on this important issue were lacking); and (4) the CHD prediction by CIMT was inferior to that by ultrasonography-assessed carotid plaque because plaque may be more representative of atherosclerosis than CIMT. (Arterioscler Thromb Vasc Biol. 2010;30:182-185.)

Key Words: carotid intima-media thickness ■ stroke ■ coronary heart disease risk ■ ultrasonography

The widespread clinical application of B-mode ultrasonographic measurement of carotid intima-media thickness (CIMT) for stratifying cardiovascular risk in primary prevention is secondary to the epidemiological evidence that increased CIMT is a worthwhile predictor of subsequent coronary heart disease (CHD) and stroke, the two leading causes of cardiovascular death.1 The present study attempts to provide an analysis of epidemiological data towards the value of CIMT for predicting CHD and stroke. Special attention is given to the added predictive value of these data, beyond traditional risk factors, and their comparative prognostic performance, vs more representative measures of atherosclerosis such as ultrasonographic-assessed plaques.

Cardiovascular Risk of CIMT

Table 1 and Table 2 summarize the data of the main prospective studies, mostly in the general asymptomatic middle-aged to older population, for whom CIMT was measured at baseline and a follow-up for the clinical event was provided.2-12 When CIMT was measured in the common carotid segment alone2-9 (Table 1), the absolute yearly risk of the event (ie, the ratio of number of events by study person-time, associated with increased CIMT greater than the arbitrary cutoff, depending on the study analyzed) ranged from 0.7% to 2.2% for CHD (myocardial infarction),2-6 from 0.4% to 1.8% for stroke,3,4,6-8 and from 1.8% to 3.2% for total cardiovascular disease.6,9 Also, the relative risk of high vs low CIMT in the common carotid,2-9 adjusted for age and sex in most studies, ranged from 1.4 to 3.2 for myocardial infarction2-6 and from 2.3 to 3.5 for stroke,3,4,6-8 suggesting that the CIMT prediction may be better for stroke than for CHD. The relative risk reached 2.3 for total cardiovascular disease6,9 (Table 1). When CIMT was measured at multiple sites (average of common carotid, bifurcation, and internal carotid measures), the absolute yearly risk of CHD10 (myocardial infarction) associated with increased CIMT above 1 mm was 1.3% and 1.4% in men and women, respectively; for stroke,11 the risk was 0.5% in either sex (Table 2). Also, the relative risk of high vs low CIMT, measured at multiple sites and adjusted for age and race, was 1.8 and 5.1 for CHD10 (myocardial infarction) and 2.0 and 3.3 for stroke11 in men and women, respectively (Table 2), suggesting that CIMT better predicted the risk of CHD and stroke in women than in men. Last, the relative risk of high...
vs low CIMT measured at multiple sites and adjusted for age and sex in elderly people was 2.9 for cardiovascular death\(^\text{12}\) (Table 2). The relative risks for any event decreased slightly, while remaining highly significant, after adjusting for conventional risk factors.\(^\text{2–12}\) These overall findings were confirmed and reinforced by a meta-analysis of 8 trials on CIMT,\(^\text{13}\) including 37,197 asymptomatic subjects who were followed up for a mean of 5.5 years. In brief, the meta-analysis showed that a CIMT increment of 0.1 mm increased the risk of myocardial infarction by 10% to 15% and increased the risk of stroke by 13% to 18%, after adjusting for age and sex. Therefore, CIMT predicts CHD and stroke independently of age, sex, race, and conventional risk factors. Moreover, the CIMT prediction for both events may be better in women than in men and the CIMT prediction may be better for stroke than for CHD when CIMT is measured in the common carotid alone. However, the CIMT prediction for CHD is relatively modest when looking at the absolute risk associated with increased CIMT, mostly between 1% and 2% per year. Therefore, the possibility that increased CIMT may requalify at a higher level the CHD risk of individuals considered at intermediate risk (1%–2% per year) on the basis of risk factors may be questioned.

### Added Value of CIMT on Prediction of Cardiovascular Risk by Risk Factors

The fact that CIMT may provide additional prognostic information to that of conventional risk factors is pivotal in discussing its clinical utility in primary prevention\(^\text{1,14}\) and is not supported by current available data. Indeed, the Multi-Ethnic Study of Atherosclerosis\(^\text{9}\) in subjects aged 45 to 84 years, who were initially free of cardiovascular disease, had a mean follow-up of 5.5 years. In brief, the meta-analysis showed that a CIMT increment of 0.1 mm increased the risk of myocardial infarction by 10% to 15% and increased the risk of stroke by 13% to 18%, after adjusting for age and sex. Therefore, CIMT predicts CHD and stroke independently of age, sex, race, and conventional risk factors. Moreover, the CIMT prediction for both events may be better in women than in men and the CIMT prediction may be better for stroke than for CHD when CIMT is measured in the common carotid alone. However, the CIMT prediction for CHD is relatively modest when looking at the absolute risk associated with increased CIMT, mostly between 1% and 2% per year. Therefore, the possibility that increased CIMT may requalify at a higher level the CHD risk of individuals considered at intermediate risk (1%–2% per year) on the basis of risk factors may be questioned.

### Table 1. Risk of MI, Stroke, and CVD Associated With CIMT Measured in the CCA in Main Prospective Studies in the General Population

<table>
<thead>
<tr>
<th>Study</th>
<th>Event Follow-Up, y</th>
<th>Sex/Age, y</th>
<th>CCA Measure</th>
<th>Absolute Risk, %/y (Positive Test Result for CIMT)</th>
<th>Relative Risk (95% CI) [Hazard Ratio for CIMT]</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIHD(^\text{10})</td>
<td>1.0 (MI)</td>
<td>M/42–60</td>
<td>Maximum</td>
<td>2.2 (&gt;1mm)</td>
<td>2.2 (0.7–6.7) [CIMT ≥1 vs &lt;1 mm]*</td>
</tr>
<tr>
<td>ROT(^\text{3})</td>
<td>2.7 (MI)</td>
<td>M/F/≥55</td>
<td>Mean</td>
<td>0.7 (&gt;0.91 mm and 80th percentile)</td>
<td>1.4 (1.2–1.8) [per 0.16-mm CIMT, 1 SD]†</td>
</tr>
<tr>
<td>CHS(^\text{4})</td>
<td>6.2 (MI)</td>
<td>M/F/45–64</td>
<td>Mean</td>
<td>1.6 (&gt;1.18 mm and 5th quintile)</td>
<td>3.2 (2.0–5.1) [5th vs 1st CIMT quintile]†</td>
</tr>
<tr>
<td>MDCS(^\text{5})</td>
<td>7.0 (MI)</td>
<td>M/F/46–68</td>
<td>Mean</td>
<td>NA</td>
<td>2.1 (1.2–3.4) [3rd vs 1st CIMT tertile]†</td>
</tr>
<tr>
<td>CAPS(^\text{6})</td>
<td>4.2 (MI)</td>
<td>M/F/19–90</td>
<td>Mean</td>
<td>2.1 (&gt;0.79 mm and 4th quartile)</td>
<td>2.2 (1.9–4.0) [4th vs 1st CIMT quartile]†</td>
</tr>
<tr>
<td>ROT(^\text{3})</td>
<td>2.7 (stroke)</td>
<td>M/F/≥55</td>
<td>Mean</td>
<td>0.8 (&gt;0.91 mm and 80th percentile)</td>
<td>1.4 (1.3–1.8) [per 0.16-mm CIMT, 1 SD]†</td>
</tr>
<tr>
<td>CHS(^\text{4})</td>
<td>6.2 (stroke)</td>
<td>M/F/≥65</td>
<td>Mean</td>
<td>1.5 (&gt;1.18 mm and 5th quintile)</td>
<td>2.8 (1.8–4.2) [5th vs 1st CIMT quintile]†</td>
</tr>
<tr>
<td>CAPS(^\text{6})</td>
<td>4.2 (stroke)</td>
<td>M/F/19–90</td>
<td>Mean</td>
<td>1.1 (&gt;0.79 mm and 4th quartile)</td>
<td>2.3 (0.9–6.3) [4th vs 1st CIMT quartile]†</td>
</tr>
<tr>
<td>MDCS(^\text{7})</td>
<td>7.0 (stroke)</td>
<td>M/F/46–68</td>
<td>Mean</td>
<td>0.4 (&gt;0.81 mm)</td>
<td>3.0 (1.6–5.7) [3rd vs 1st CIMT quartile]†</td>
</tr>
<tr>
<td>Kitamura et al(^\text{8})</td>
<td>4.5 (stroke)</td>
<td>M/60–74</td>
<td>Maximum</td>
<td>1.3 (&gt;1.07 mm and 4th quartile)</td>
<td>3.5 (1.3–9.5) [4th vs 1st CIMT quintile]†</td>
</tr>
<tr>
<td>MESA(^\text{9})</td>
<td>5.3 (CVD)</td>
<td>M/F/45–84</td>
<td>Maximum</td>
<td>1.8 (&gt;0.97 mm and 4th quartile)</td>
<td>2.3 (1.4–3.8) [4th vs 1st CIMT quartile]‡</td>
</tr>
<tr>
<td>CAPS(^\text{6})</td>
<td>4.2 (CVD)</td>
<td>M/F/19–90</td>
<td>Mean</td>
<td>3.2 (&gt;0.79 mm and 4th quartile)</td>
<td>2.3 (1.4–3.8) [4th vs 1st CIMT quartile]‡</td>
</tr>
</tbody>
</table>

CAPS indicates Carotid Atherosclerosis Progression Study; CCA, common carotid artery; CHS, Cardiovascular Health Study; CI, confidence interval; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; KIHD, Kuopio Ischemic Heart Disease study; MDCS, Malmo Diet and Cancer Study; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; NA, not available; ROT, Rotterdam Study.

*Age and race adjusted.
†Age and sex adjusted.
‡Nonadjusted.
disease, and who were followed up for 5.3 years showed that the area under the receiver operating characteristic curve (AUC) did not increase significantly after adding CIMT to multiple risk factors in the prediction model for cardiovascular disease and in the model for CHD (AUC of 0.78 for risk factors plus CIMT vs 0.77 for risk factors alone, in both models). Similarly, another small case-control study found that incorporating the IMT measure with the Framingham risk score did not increase the AUC for coronary events in subjects at low vs intermediate risk (0.69 vs 0.66). However, judging the prognostic performance of an emerging risk biomarker, such as CIMT, by c statistics alone may be misleading because in the presence of a fairly robust risk score, as provided by the Framingham algorithm, most biomarkers cannot substantially increase the c statistic or the AUC. Furthermore, data are lacking on the added value of CIMT for predicting stroke with regard to conventional risk, which is regrettable knowing that CIMT, when measured in the common carotid alone, may be superior in predicting risk of stroke than in predicting risk of CHD (Table 1). Therefore, more research is needed to statistically evaluate the incremental value of CIMT in the prediction of CHD and overall stroke.

**Compared Prognostic Performance of CIMT and Carotid Plaque**

Previously, the ultrasonographic phenotyping of carotid atherosclerosis was determined primarily by measurement of CIMT. In the past few years, several groups have shown that carotid total plaque presence or plaque area is more closely related to coronary artery disease, and is more strongly predictive of coronary events than IMT. It is now apparent that different ultrasonographic phenotypes of atherosclerosis, such as IMT, plaque area, and stenosis, are biologically and genetically distinct. In multivariable linear regression, traditional coronary risk factors explain only 15% to 17% of IMT, as assessed by the R² statistic, but account for 52% of the carotid total plaque area. This suggests that the carotid plaque area is more representative of atherosclerosis than IMT. In particular, CIMT in the far wall of the common carotid, avoiding plaque, may include vascular remodeling and early atherosclerosis.

**Study and Clinical Implications**

First, the reported risks were hardly comparable because of the following of the cited studies including the following: (1) the site of CIMT measure (in the far wall or in the far and near wall of the single common carotid or the common carotid, bifurcation, and internal carotid); (2) the inconsistent incorporation of a nonobstructive carotid plaque in the CIMT measure; (3) the use of mean or maximum CIMT; (4) the report of adjusted or unadjusted models; and (5) the arbitrary cutoff point to evaluate the CIMT ability to predict risk. Second, the lesser data on the added value of CIMT for predicting stroke than for predicting CHD beyond conventional risk factors are prejudicial to larger use of CIMT for predicting the risk of stroke. Third, the transferability of the prognostic value of CIMT, mostly obtained in middle-aged or older subjects, to younger populations in whom data on CIMT are insufficient, except in the Carotid Atherosclerosis Progression Study, should be questioned.

In conclusion, whether and how to clinically use CIMT for predicting cardiovascular risk is a hot topic of debate. Despite much epidemiological data on the prognostic performance of CIMT, there is no clear evidence that CIMT measurement may improve CHD prediction by risk factors and really change the risk of CHD assigned to an individual. There are also insufficient data supporting the possibility that CIMT may improve stroke prediction beyond prediction by conventional risk factors (Table 2). Therefore, more research is needed to further standardize CIMT imaging, to better assess the prognostic value of CIMT in young populations in whom data are insufficient, and to evaluate in more detail the incremental value for CIMT in risk prediction of CHD and stroke beyond traditional risk factors and other bioimaging of atherosclerosis.

**Disclosures**

None.

**References**


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Arterioscler Thromb Vasc Biol. 2010;30:182-185; originally published online November 30, 2009;
doi: 10.1161/ATVBAHA.109.196980
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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