Vascular Biomarkers in the Prediction of Clinical Cardiovascular Disease
The Strong Heart Study

Mary J. Roman, Jorge R. Kizer, Lyle G. Best, Elisa T. Lee, Barbara V. Howard, Nawar M. Shara, Richard B. Devereux

Abstract—We compared the ability of separately measured intimal-medial thickness and atherosclerotic plaque to predict incident cardiovascular disease. American Indian men and women from the Strong Heart Study who were free of cardiovascular disease were evaluated with carotid ultrasound and cardiovascular disease risk factor assessment. End-diastolic intimal-medial thickness of the common carotid arteries was measured and averaged. Arterial mass (cross-sectional area) was calculated from intimal-medial thickness and end-diastolic diameter. Atherosclerosis was defined by focal plaque (discrete thickening \( >50\% \) relative to the adjacent wall) and the number of carotid segments containing plaque (plaque score); 2441 participants (age 63\( \pm \)8 years) were followed-up for a mean of 7.7\( \pm \)2.8 years, during which time 495 experienced incident cardiovascular disease events. Time-to-event analyses were performed in groups stratified according to diabetes and hypertension status. Cardiovascular disease events were predicted by presence and extent of atherosclerosis in all groups; intima-medial thickness and arterial mass were only associated with outcomes when neither hypertension nor diabetes was present. Unequivocal evidence of atherosclerosis (plaque) and its extent (plaque score) are independently associated with incident cardiovascular disease events in individuals without preexisting cardiovascular disease regardless of diabetes and hypertension status. Hypertension-related increases in intima-media thickness and arterial mass appear to limit their use as measures of early or diffuse atherosclerosis and, hence, association with cardiovascular disease outcomes. These findings support the utility of separate assessment of focal atherosclerosis and intimal-medial thickness in epidemiological studies, trials, and risk stratification protocols. (Hypertension. 2012;59:29-35.)

Key Words: cardiovascular disease prognosis ■ carotid arteries ■ epidemiological methods

Duplex carotid ultrasonography traditionally has been used as a clinical tool to evaluate the presence of significant stenosis in the setting of asymptomatic carotid bruit or clinical cerebrovascular disease. More recently, the technique has been utilized in epidemiological studies to detect subclinical vascular disease (intimal-medial thickness [IMT] and nonobstructive plaque) and to assess its relation to cardiovascular disease (CVD) risk factors and prevalent and incident cardiovascular disease.1 Studies examining the prognostic value of carotid ultrasonography have varied in methodology. Importantly, IMT and plaque have not always been separately evaluated. Focal plaque is a direct manifestation of atherosclerosis, whereas IMT has been considered a measure of diffuse or early atherosclerosis. However, IMT is increased by hypertension because of medial hypertrophy unrelated to atherosclerosis2 and is not increased in chronic inflammatory diseases despite markedly premature subclinical (and clini-
cal) atherosclerosis manifest by focal plaque.3–5 Thus protocols reporting wall thicknesses that incorporate focal plaque thickness confine the 2 entities and thereby potentially overstate the prognostic importance of IMT.

Although a number of studies have separately examined IMT and plaque in relation to CVD outcomes, several limitations are noteworthy. Multivariable analyses including standard CVD risk factors have not always been performed to examine the independent or additive associations of carotid ultrasound findings.6–8 Some studies have limited CVD events to either myocardial infarction6,9,10 or stroke.11,12 Other studies have examined combined carotid and femoral artery IMT7,8 or have used study-specific internal reference values of multiple averaged IMT segments.13 Thus, the present study was designed to evaluate the separate prognostic associations of definite carotid atherosclerosis (presence and extent of plaque) and common carotid artery (CCA) wall thickness

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Blood pressures were obtained in the seated position from the right brachial artery after 5 minutes of rest by trained personnel using an automated sphygmomanometer. Hypertension was defined as previously described.16 Blood pressures were never obtained at the level of a discrete plaque. Plaque score, a semiquantitative measure of the extent of atherosclerosis,21,25,26 was calculated by the number of left and right segments (common carotid, bulb, internal carotid, external carotid) containing plaque; thus, plaque score ranged from 0 to 8.

Subjects and Methods

Study Population

The Strong Heart Study is a population-based longitudinal study of prevalent and incident CVD and its risk factors in American Indians that began in 1989. Details of the study design have been previously published.16,17 At the third examination in 1997 to 1999, carotid ultrasonography was added to the study protocol. A total of 2441 participants were free of prevalent clinical CVD at the time of examination (2.4%). Diabetes was present in 52.2% of the population, of whom 69% were using antihypertensive medications. Use of lipid-lowering therapy was uncommon at the time of examination (2.4%). Diabetes was present in 47.6% of the population, and 27.4% were active smokers. Among the 2441 participants, 495 (20.3%) experienced initial fatal and nonfatal CVD events (101 myocardial infarction, 204 definite coronary heart disease, 92 stroke, 98 congestive heart failure) during a mean follow-up of 7.7±2.8 years; 21.4% of initial events were fatal.

Traditional CVD risk factors, vascular biomarkers, and CVD outcomes are compared in Tables 1 and 2 stratified according to diabetes and hypertension status. Ages were higher and renal function was lower in the 2 groups with hypertension compared to the other 2 groups. Body mass index and waist circumference were higher and rates of smoking were lower in the groups with hypertension and/or diabetes compared to the normal group. Body mass index and waist circumference were also significantly higher in the 2 groups with diabetes compared to the group with hypertension alone. The proportion of men was lowest in those with both hypertension and diabetes. The 4 groups were compa-
Arterial mass was associated with outcomes in either model of hypertension nor diabetes. However, neither IMT nor broader adjusted models in the group with neither IMT nor broader adjusted models in the group with neither hypertension and/or diabetes. In contrast, atherosclerotic plaque and plaque score were associated with outcomes in all 4 groups. In secondary analyses, adding use of antihypertensive or glucose-lowering medications to multivariable analyses did not substantially alter results (data not shown).

In the entire population, the C-statistic for prediction of events by risk factors alone (0.700; 95% CI, 0.674–0.726) was significantly increased by addition of either plaque (C-statistic=0.714; 95% CI, 0.688–0.739; \( P=0.011 \)) or plaque score (C-statistic=0.719; 95% CI, 0.694–0.744; \( P=0.001 \)) to the model. In view of the significant effect modification observed for carotid IMT by hypertension and diabetes status, wherein carotid IMT was only predictive of outcome in the normal group, receiver-operator characteristic curve analyses using IMT were restricted to this group. Although addition of IMT substantially increased the magnitude of the C-statistic compared to the risk factor model alone (from 0.735 [95% CI, 0.678–0.791] to 0.748 [95% CI, 0.690–0.806], the change was not statistically significant (\( P=0.198 \)).

To determine whether carotid IMT might be more predictive of incident stroke or coronary artery disease than plaque, we performed additional analyses in the entire group because in the groups with hypertension and/or diabetes. In contrast, atherosclerotic plaque and plaque score were associated with outcomes in all 4 groups. In secondary analyses, adding use of antihypertensive or glucose-lowering medications to multivariable analyses did not substantially alter results (data not shown).

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### Table 1. Comparison of Demographic Variables and Cardiovascular Disease Risk Factors Stratified According to Diabetes and Hypertension Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>No HTN or DM (n=734)</th>
<th>HTN Alone (n=545)</th>
<th>DM Alone (n=432)</th>
<th>HTN and DM (n=730)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.1±7.5</td>
<td>64.6±8.4*</td>
<td>61.9±6.9</td>
<td>63.2±7.2†</td>
</tr>
<tr>
<td>Male, %</td>
<td>39.2</td>
<td>38.0</td>
<td>32.2</td>
<td>29.5*</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.2±6.2</td>
<td>30.7±6.0*</td>
<td>32.1±6.8*</td>
<td>33.4±6.8*</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>100±15</td>
<td>104±14*</td>
<td>108±15*</td>
<td>111±15*</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>37.9</td>
<td>27.1*</td>
<td>27.3‡</td>
<td>17.2*</td>
</tr>
<tr>
<td>Systolic pressure, mm Hg</td>
<td>120±11</td>
<td>143±19*</td>
<td>121±11</td>
<td>139±21*</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>99±11</td>
<td>100±11</td>
<td>191±75*</td>
<td>184±67*</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mg/dL</td>
<td>147±39</td>
<td>146±39</td>
<td>143±39</td>
<td>145±39</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>45±14</td>
<td>46±15</td>
<td>39±10*</td>
<td>43±13*</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>127±74</td>
<td>140±86</td>
<td>167±132*</td>
<td>171±129*</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m²</td>
<td>86±16</td>
<td>79±22*</td>
<td>86±21</td>
<td>78±26*</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HTN, hypertension.

*\( P<0.001 \), †\( P<0.05 \), ‡\( P<0.005 \), §\( P<0.01 \) vs no HTN or DM group.

### Table 2. Comparison of Vascular Biomarkers and Cardiovascular Disease Outcomes Stratified According to Diabetes and Hypertension Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>No HTN or DM (n=734)</th>
<th>HTN Alone (n=545)</th>
<th>DM Alone (n=432)</th>
<th>HTN and DM (n=730)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intimal-medial thickness, mm</td>
<td>0.72±0.14</td>
<td>0.75±0.15‡</td>
<td>0.75±0.16§</td>
<td>0.76±0.15*</td>
</tr>
<tr>
<td>Arterial mass, mm²</td>
<td>15.03±4.12</td>
<td>16.14±4.27*</td>
<td>16.10±4.49*</td>
<td>16.59±4.27*</td>
</tr>
<tr>
<td>Atherosclerotic plaque, %</td>
<td>57.2</td>
<td>66.4‡</td>
<td>66.4†</td>
<td>66.2†</td>
</tr>
<tr>
<td>Plaque score</td>
<td>1.2±1.4</td>
<td>1.6±1.7*</td>
<td>1.4±1.4</td>
<td>1.6±1.7*</td>
</tr>
<tr>
<td>Incident CVD, n (%)</td>
<td>74 (10.1)</td>
<td>97 (17.8§)</td>
<td>110 (25.5)*</td>
<td>214 (29.3)*</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease; DM, diabetes mellitus; HTN, hypertension.

*\( P<0.001 \), †\( P<0.05 \), ‡\( P<0.005 \), §\( P<0.01 \) vs no HTN or DM group.
of the relatively small number of separate events in the 4 subgroups. Multivariable analyses adjusting for the covariates listed in Table 3 as well as for the presence or absence of diabetes and hypertension indicated that IMT was not an independent predictor of either coronary heart disease or of stroke, whereas atherosclerotic plaque was a strong independent predictor of coronary heart disease (heart rate, 1.88; 95% CI, 1.35–2.61; P<0.001) and plaque score was an independent predictor of stroke (heart rate, 1.19; 95% CI, 1.04–1.35; P=0.012).

**Discussion**

Our study shows that the presence and extent of carotid plaque, direct manifestations of atherosclerosis, are strong predictors of incident CVD, independent of the effects of diabetes, hypertension, and other established risk factors. Importantly, our findings are adjusted for both traditional CVD risk factors as well as estimated glomerular filtration rate, itself a potent predictor of CVD risk. In contrast, CCA IMT and arterial mass (cross-sectional area) were only predictive of CVD outcome in Strong Heart Study participants without diabetes and, particularly, hypertension. Our findings suggest that, in the absence of hypertension, these 2 vascular biomarkers may represent arterial wall thickening associated with atherosclerosis. In contrast, hypertension-associated medial hypertrophy 2,21 is not independently related to CVD outcomes.

Studies that have analyzed IMT and plaque separately generally show the greatest risk of future CVD events to be conferred by the presence of focal plaque. In one of the first such studies, 2000 healthy subjects aged 30 to 70 years were followed-up for 6 years after baseline carotid and femoral ultrasound examination. Cardiovascular events occurred in 5.5% of those with increased IMT (diffuse thickening >1 mm) and in 18.4% of those with plaque (focal thickening of IMT >2 mm). Similarly, in 10 000 healthy individuals followed-up for 10 years in the Cafes-Caves Study, incident CVD occurred in 8.6% of those with increased IMT and in 39.3% of those with plaque.8 However, neither of these studies adjusted for CVD risk factors. In the Kuopio Ischemic Heart Disease Risk Factor Study of 2,181 middle-aged Finnish men, the 4-year risk of acute myocardial infarction was increased 2.1-fold in those with increased IMT (>1 mm) and 3.4-fold in those with nonobstructive plaque in comparison to those with normal carotid ultrasound studies;9 again, results were not adjusted for CVD risk factors.

Three recent analyses in population-based studies separately examined IMT and plaque in relation to outcomes and adjusted for CVD risk factors. Among 1249 participants aged 18 to 99 years in the San Daniele Study, a town in northeastern Italy, the relative risk of ischemic cerebrovascular events (ischemic stroke or transient ischemic attack) was 5.6 (95% CI, 2.2–18.1) for IMT (mean >1.9 mm) as compared to those with normal IMT and no plaque at baseline examination.10,11 The analyses included those with prevalent CVD at baseline, and data were not available from the baseline examination to examine IMT as a continuous measure.

In the Atherosclerosis Risk in Communities Study, categories (<25th percentile, 25th to 75th percentile, >75th percentile) of averaged CCA, bifurcation, and internal carotid artery IMT and plaque were added to the Atherosclerosis Risk in Communities 10-year coronary risk score in 13 145 participants without prevalent CVD at baseline.12 The area under the receiver-operating characteristic curve significantly improved when plaque, but not IMT, was added to traditional risk factors in women. Although both plaque and IMT increased the area under the receiver-operating characteristic curve in men, the increase was greater for IMT than plaque.

<table>
<thead>
<tr>
<th>Vascular Biomarker</th>
<th>No HTN or DM HR (95% CI)</th>
<th>P</th>
<th>HTN Alone HR (95% CI)</th>
<th>P</th>
<th>DM Alone HR (95% CI)</th>
<th>P</th>
<th>HTN and DM HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT, per SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted and sex-adjusted model</td>
<td>1.29 (1.05–1.59)</td>
<td>0.017</td>
<td>0.95 (0.78–1.16)</td>
<td>0.616</td>
<td>1.16 (0.98–1.38)</td>
<td>0.087</td>
<td>0.96 (0.84–1.10)</td>
<td>0.576</td>
</tr>
<tr>
<td>Multivariable model</td>
<td>1.26 (1.01–1.57)</td>
<td>0.041</td>
<td>0.96 (0.78–1.17)</td>
<td>0.681</td>
<td>1.10 (0.92–1.31)</td>
<td>0.311</td>
<td>0.96 (0.84–1.10)</td>
<td>0.555</td>
</tr>
<tr>
<td>Arterial mass, SD</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age-adjusted and sex-adjusted model</td>
<td>1.42 (1.15–1.74)</td>
<td>0.001</td>
<td>1.16 (0.95–1.42)</td>
<td>0.142</td>
<td>1.16 (0.97–1.39)</td>
<td>0.103</td>
<td>1.06 (0.91–1.22)</td>
<td>0.463</td>
</tr>
<tr>
<td>Multivariable model</td>
<td>1.39 (1.11–1.73)</td>
<td>0.004</td>
<td>1.11 (0.90–1.36)</td>
<td>0.331</td>
<td>1.12 (0.92–1.36)</td>
<td>0.270</td>
<td>1.04 (0.90–1.22)</td>
<td>0.558</td>
</tr>
<tr>
<td>Atherosclerotic plaque</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted and sex-adjusted model</td>
<td>2.53 (1.39–4.60)</td>
<td>0.002</td>
<td>1.79 (1.07–3.00)</td>
<td>0.026</td>
<td>1.71 (1.08–2.72)</td>
<td>0.023</td>
<td>2.66 (1.87–3.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable model</td>
<td>2.26 (1.25–4.10)</td>
<td>0.007</td>
<td>1.74 (1.06–2.86)</td>
<td>0.030</td>
<td>1.26 (0.80–1.99)</td>
<td>0.319</td>
<td>2.14 (1.50–3.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plaque score, per segment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted and sex-adjusted model</td>
<td>1.42 (1.23–1.63)</td>
<td>&lt;0.001</td>
<td>1.21 (1.08–1.36)</td>
<td>&lt;0.001</td>
<td>1.30 (1.14–1.48)</td>
<td>&lt;0.001</td>
<td>1.34 (1.25–1.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable model</td>
<td>1.41 (1.23–1.63)</td>
<td>&lt;0.001</td>
<td>1.17 (1.05–1.30)</td>
<td>0.006</td>
<td>1.26 (1.10–1.43)</td>
<td>0.001</td>
<td>1.22 (1.13–1.31)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; IMT, intimal-medial thickness; SD, standard deviation.

*Multivariable models are adjusted for age, sex, body mass index, waist circumference, current smoking, non-HDL cholesterol, HDL cholesterol, triglycerides, and estimated glomerular filtration rate. The nonhypertensive groups are additionally adjusted for fasting glucose.
Because this study evaluated averaged IMT measured from areas that might include plaque in the IMT measurement, it is possible that the significance of IMT in relation to outcomes is overstated. The extent of atherosclerosis, ie, the prevalence of plaques in multiple segments, was not examined in relation to outcome.

In 2965 members of the Framingham Offspring Study cohort followed-up for 7.2 years, mean IMT of the CCA, maximum IMT of the internal carotid artery, and plaque within the internal carotid artery (defined as IMT >1.5 mm) were all associated with incident cardiovascular events. Only the internal carotid artery IMT and plaque resulted in an increase in the C-statistic generated by consideration of the Framingham risk score. The present study confirms this observation for both the presence and the extent of atherosclerosis. Similarly to the Framingham Offspring Study, the C-statistic was not significantly improved by addition of common carotid IMT in our study. However, our group of normal participants (no hypertension or diabetes) is relatively small and lacks sufficient power for assessment of the incremental discriminatory value of this measure. Larger studies of healthy individuals will be necessary to determine whether the increased magnitude of the C-statistic achieved by carotid IMT suggested here in fact represents genuine improvement in risk prediction.

An indirect validation of the superiority of carotid plaque over carotid IMT is provided by the substantially stronger relation of carotid plaque area to significant underlying coronary artery disease as evidenced by computed tomography angiography. Similarly, right carotid artery plaque area were more strongly related to incident myocardial infarction and ischemic stroke than carotid IMT in the Tromsø Study. These results are of particular interest because IMT measurement could incorporate plaque thickness if plaque was present in the predefined area where IMT measurements were performed. Although plaque area derived from a 2-dimensional ultrasound study may not be a precise measure of atherosclerosis burden, these findings are similar to those using the semiquantitative plaque score in the present study. The Rotterdam Study found IMT and plaque (evaluated as none vs at least 3 plaques using a plaque score) to be equally predictive of myocardial infarction independent of traditional risk factors; the authors comment on the ease of plaque assessment compared to the precision required for IMT measurement. Furthermore, in the Rotterdam Study, increasing plaque score (0–6) increased the risk of stroke and, in a separate population of elderly men, plaque score independently predicted all-cause and cardiovascular mortality.

There are several potential limitations to our study. In the Strong Heart Study, IMT was only measured in the distal CCA. Data from the Cardiovascular Health Study and the British Regional Heart Study suggest a stronger association of CCA IMT with prevalent stroke, whereas bifurcation or internal carotid artery IMT were more strongly related to prevalent myocardial infarction. However, adjusted relative risks for prediction of incident events were only marginally different between the CCA and internal carotid artery IMT in the Cardiovascular Health Study. A major advantage of CCA IMT is its higher measurement yield compared to other segments. In the Atherosclerosis Risk in Communities Study, IMT measurements were obtainable from the CCA in 91.4%, from the bifurcation in 77.3%, and from the internal carotid artery in 48.6% of participants. A report on 1881 Rotterdam Study participants showed a similar trend in measurement yield: 96% in the CCA, 64% in the bifurcation, and 31% in the internal carotid artery. Measurement yield of CCA IMT in the current study was comparable to that in these earlier studies (96%). The present findings derive from a cohort of American Indians at high cardiometabolic risk, such that generalizability to other populations cannot be assumed. However, stratification and adjustment showed that the presence and extent of atherosclerosis were associated with incident CVD independent of diabetes and hypertension and other risk factors. Furthermore, the same traditional risk factors for cardiovascular disease in the general U.S. population have been shown to be operative in the Strong Heart Study population. Although one cannot necessarily extrapolate results from this generally obese and insulin-resistant population to nonobese noninsulin-resistant populations, our findings will be applicable to a greater proportion of the broader population if current trends in the increasing prevalence of obesity and diabetes continue unabated.

Perspectives

The present study shows that unequivocal evidence of atherosclerosis (plaque) and its extent (plaque score) are independently associated with first incident CVD events in individuals, regardless of diabetes and hypertension status. In contrast, IMT and arterial mass were only found to be associated with CVD outcome in the absence of diabetes and hypertension, likely attributable to hypertension-mediated vascular hypertrophy, lessening the likelihood that diffuse vessel wall thickening and lumen dilatation are manifestations of atherosclerosis. These findings highlight the value of plaque as a vascular biomarker and support the utility of separate assessment of focal atherosclerosis and IMT in epidemiological studies, as well as risk assessment protocols. Whether these direct measures of atherosclerosis afford
improved risk prediction in selected subgroups warrants further study in larger samples.

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Disclosures
None.

References


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