Evaluation of the Associations Between Carotid Artery Atherosclerosis and Coronary Artery Stenosis

A Case-Control Study

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To evaluate the consistency, strength, and independence of the relation of carotid atherosclerosis to coronary atherosclerosis, we quantified coronary artery disease risk factors and extent of carotid atherosclerosis (B-mode score) in 343 coronary artery disease patients and 167 disease-free control patients. In univariable analyses, there was a strong association between coronary status and extent of carotid artery disease in men and women older than and younger than 50 years ($p < 0.001$ for men and women $> 50$ years, $p < 0.001$ for women $\leq 50$ years, $p = 0.045$ for men $\leq 50$). The relation remained strong after control for age in men and women older than 50 years and in women younger than 50 ($p < 0.001$ for men and women $> 50$ years, $p = 0.003$ for women $\leq 50$) but did not persist after control for age in men younger than 50. Logistic models that included coronary disease risk factors, with or without B-mode score, as independent variables and presence or absence of coronary disease as the outcome variable indicated that the extent of carotid atherosclerosis was a strong, statistically significant independent variable in models for men and women older than 50 years of age. Next, we examined the usefulness of B-mode score as an aid in screening for coronary artery disease in men and women older than 50 years. Classification rules, both including and excluding B-mode score, were developed based on logistic regression and, for comparison, recursive partitioning (decision trees). The performance of these rules and the bias of their performance statistics were estimated. The improved classification of the study sample when B-mode score was incorporated in the rule was statistically significant only for men ($p = 0.015$). However, the addition of B-mode score was found to 1) increase the median discrimination score for both sex groups based on the logistic model, and 2) yield better sensitivities and specificities for rules based on recursive partitioning. Thus B-mode score is strongly, consistently, and independently associated with coronary artery disease in patients older than 50 and is at least as useful as well-known risk factors for identifying patients with coronary artery disease. (Circulation 1990;82:1230–1242)

A number of population-based studies have identified interrelations between symptoms and signs of carotid artery disease and coronary artery disease (CAD). Cohort studies have shown an increased risk of cerebrovascular disease (stroke) in individuals with signs and symptoms of CAD compared with nonaffected individuals.1,2 Symptoms and signs of cerebrovascular disease, particularly transient ischemic attack,3-4 carotid bruit,5-8 and completed stroke9 also identify individuals with a greater-than-normal likelihood of developing a coro-

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nary event. Furthermore, statistically significant Pearson correlations between atherosclerosis of the coronary and carotid arteries (range, 0.4–0.5) have been noted in three autopsy studies.10–12 The correlation of coronary atherosclerosis and intracranial cerebral arterial atherosclerosis may be slightly better.13 We have previously demonstrated that presence or absence of coronary disease helps explain variability in carotid artery atherosclerosis.14,15 Others have found evidence for CAD (by exercise testing6,17 or coronary angiography18) in patients with symptomatic cerebrovascular disease. Studies of 343 individuals with and 167 individuals without CAD allowed us to test for associations between asymptomatic carotid artery atherosclerosis and CAD. The associations developed also allowed us to test a quantitative measure of extent of extracranial carotid atherosclerosis for its usefulness in classifying CAD cases and controls.

Methods

The approach to accessing patients for this study has been previously described.14,15 In brief, patients hospitalized for coronary angiography were asked to participate in an ongoing study of risk factors of coronary artery atherosclerosis and an ultrasound evaluation of the carotid arteries. The study group consisted of all patients who provided informed consent and who had 50% or more stenosis of one or more coronary arteries (cases) or who had normal coronary arteries (controls). Seventy-three percent of the control population underwent coronary angiography because of chest pain, and angiograms were performed on 20% in the course of evaluation of valvular heart disease. The remainder underwent angiography for evaluation of arrhythmia, heart failure, congenital heart disease, or other problems. Because the vast majority of patients admitted to the hospital for coronary angiography are male cases older than 50 years, the design of the study of risk factors for coronary disease was to select patients by random sampling stratified by gender and age. We accessed 100% of male controls older than 50 years free of coronary disease, and 100% of female cases and controls older than 50 years as well. In addition, random samples of male and female cases and controls younger than 50 were chosen. Stratification by age (50 years) was chosen, also, to allow us to examine differences in patterns of CAD risk factors in older compared with younger individuals. Exclusion criteria included factors that may alter our ability to interpret plasma lipid and lipoprotein concentrations (liver or kidney disease, alcohol abuse, treatment with heparin, cortisone, or lipid-lowering drugs, thyroid disease, and recent heart attack) or our ability to interpret the coronary angiogram (resulting in elimination of individuals who had undergone coronary bypass surgery or angioplasty). Patients with stroke, transient ischemic attack, endarterectomy, and aortic valve disease were also excluded. The latter patients were eliminated because extent of carotid atherosclerosis was greater in the small number of individuals older than 50 with aortic valve disease compared with aortic disease–free controls. After providing informed consent, subjects were administered a standard questionnaire for evaluation of angina pectoris and other symptoms and risk factors associated with cardiovascular disease. They also underwent an abbreviated physical examination (height, weight, blood pressure, and auscultation of the heart for murmurs and of the carotid and femoral arteries for bruits). Blood for assay of glucose, lipid, and lipoprotein concentrations was drawn from fasting patients the morning of catheterization.

Evaluation of Vascular Status

Extent of carotid atherosclerosis was evaluated by a modification of a method previously detailed.19 For this, the left and right carotid arteries of patients were evaluated in the anterior oblique, lateral, and posterior oblique planes using a Biosound compact real-time (B-mode) imager with an 8-MHz mechanical sector scanner probe and digital scan converter. A carotid artery B-mode “score” was computed for each patient in a manner similar to that previously published and represented the sum of measurements of the maximum near and far wall thickness in the low common, high common, and low internal carotid arteries on the left and right side. We eliminated the measurement of the high internal carotid artery from our computation of the B-mode score in our current work because it has become evident that the sonographer is unable to interrogate this area adequately in all patients. This did not affect the reproducibility of the carotid artery score as presented previously: the correlation coefficient for repeat determinations, with elimination of the data from the high internal carotid artery, is r>0.80.

Coronary angiography was performed by the percutaneous technique using either the Judkins or multipurpose catheters. Patients were divided into those with coronary stenosis (≥50% stenosis of any artery) or those without coronary stenosis (normal coronary artery). Patients with stenoses that obstructed the lumen by less than 50% were excluded from the study.

Evaluation of Risk Factor Variables

The candidate risk factor variables evaluated in this study included age, body mass index (Quetelet index, wt/ht²), pack-years of smoking, plasma concentrations of hemoglobin and uric acid, plasma concentrations of total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol, and low density lipoprotein (LDL) cholesterol, presence or absence of high blood pressure (coded as present if there was any history of high blood pressure or if the blood pressure measured in the hospital exceeded 150 mm Hg systolic or 95 mm Hg diastolic), diabetes mellitus (coded as present if the patient had a history of diabetes or if the fasting glucose exceeded 140 mg/dl), family history (coded as positive if a first-degree relative had a coronary event before the age
of 60 years), and left ventricular hypertrophy (coded as present according to criteria of Sokolow and Lyon20 or Romhilt and Estes21). In some analyses, the aggregate carotid artery (B-mode) score was also entered into statistical analyses. Risk factor data for all patients were collected using standardized questionnaires and clinical chemistry methods (“Coulter-S+” hematology analyzer, Hialeah, Fla., Technicon SMAC, Terrytown, N.Y.). The plasma concentration of LDL was estimated by Lipid Research Clinics methodology after ultracentrifugation of plasma at D=1.006 to float very low density lipoprotein and chylomicrons.22 LDL was calculated as the difference between the total D=1.006 infranate cholesterol and infranate HDL. Because the distribution of the plasma triglyceride concentration was skewed to the right, the logarithm (base 10) of this variable was used in analysis.

Statistical Methods

The relations between potential risk factors and CAD status and between risk factors and the extent of extracranial carotid atherosclerosis were examined using both univariable and multivariable methods within each age-sex group (women >50 years old, women ≤50 years old, men >50 years old, and men ≤50 years old). The univariable analyses consisted of t tests across CAD status for continuous factors and χ² tests of homogeneity of the factors across CAD status for dichotomous factors. The relations between B-mode score and the other factors were examined by evaluating correlations and t tests.23 Multivariable analyses were performed using logistic regression models.24 A set of “important” prognostic factors for “disease” (with CAD) or “nondisease” (without CAD) was found for each age-sex group via both forward and backward stepwise approaches (candidate risk factors included all those mentioned above). Because both approaches resulted in selection of essentially the same prognostic factors and resulted in classification rules that performed equally well, we present data from forward selection only. Variable selection was terminated when no candidates for entry were significant at p<0.05, and all those selected for entry remained significant at p<0.10. To evaluate the effect of including carotid artery (B-mode) score as an independent variable in the logistic models for the classification of subjects, this variable was forced into the models previously chosen for each age-sex group, and new regression coefficients were calculated. Model goodness of fit was assessed by the test of Hosmer and Lemeshow.25

The improvement in ability to classify patients according to CAD status associated with knowledge of the extent of extracranial carotid atherosclerosis was examined in men and women older than 50 using two methods for developing classification rules. The first method was based on the separate stepwise logistic regression models described above. The fitted logistic regression equations produced, for each subject, a predicted probability of being among the diseased group. A cutpoint-predicted probability was selected to serve as the basis for a classification rule. For each group classified, we chose a cutpoint that maximized the sum of sensitivity and specificity.26 The conditional probability of “correct classification” (conditional on the observed values of a subject’s covariates included in the model) is given by the predicted probability of disease for cases and the predicted probability of no disease for controls. Histograms of the predicted probabilities of correct classification (cases and controls grouped together) for the models into which B-mode score was not allowed to enter were compared with those into which B-mode score was forced, and the Wilcoxon signed-rank test was used to test for differences in the distributions of the predicted probabilities of correct classification for models with versus those without B-mode score. Separate histograms were also constructed for predictive probabilities of disease in cases and controls. The grouped data were used rather than the separate case and control data to decrease the number of tests performed and to increase the power of the signed-rank tests via the increased sample; the case and control histograms are available on request.

A second analysis, examining the potential of B-mode to improve classification, was undertaken whereby disease status was classified separately for men and women older than 50 by the method of recursive partitioning and the classification and regression tree (CART) algorithm.28 Recursive partitioning is a nonparametric method that can be used to classify observations into two or more groups based on a series of dichotomous “splits” of a set of prognostic factors. The classification rules produced by recursive partitioning have a simple tree structure in which individuals can be classified by responding to a set of questions concerning the explanatory variables, each of which has a yes-no answer. Breiman et al28 present the theoretical justification of recursive partitioning and classification trees in detail. The recursive partitioning algorithm gives an overall ranking of the relative importance of each variable (relative to the most important explanatory variable) for accurately classifying subjects. This summary measure of relative importance was used to evaluate the importance of B-mode score.

The relatively small number of observations for men (n=184) and women (n=142) prevented us from dividing the data into learning and test sets. Thus, sensitivities and specificities presented in the results section were estimated by reclassifying subjects after they were used to estimate model parameters (these are referred to as resubstitution estimates). McNe- mar’s χ² test for paired data29 was used to test for significant differences in the resubstitution estimates of the probability of correct classification associated with adding B-mode score to the roster of prognostic factors for both classification techniques.

Resubstitution estimates of the sensitivities and specificities are biased highly regardless of the clas-
sification technique used. Therefore, tenfold cross-validation was used to obtain less-biased estimates of sensitivity and specificity for classification rules found by recursive partitioning. For this, we divided the learning set into 10 subsets of approximately equal size, grew new trees of fixed complexity using nine subsets as a learning set, and classified the remaining subset. (This process was repeated for each subset.) Classifications of the 10 subsets were then pooled to provide a new, less-biased estimate of each tree’s misclassification rate.

Because cross-validation has been previously to be relatively unreliable for estimating bias in sensitivity and specificity estimates obtained from logistic regression models, more reliable estimates of the true misclassification rates of the logistic models were obtained by a bootstrap technique. Our application of the technique was carried out in the following manner. For each logistic regression model: 1) 200 bootstrap samples of size \( n \) were drawn from the empirical sample \( \{X_1, X_2, \ldots, X_n\} \) of subject disease status and his measured risk factors (e.g., for women \( >50 \) years old, 200 random samples of size \( n=142 \) were drawn with replacement from the originally collected data). Sampling was stratified on case-control status so that the ratio of cases to controls was fixed to equal that of the original sample; 2) using the variables selected from the previous logistic models, regression coefficients were reestimated for each bootstrap sample; 3) using the reestimated coefficients, an “optimal” cutpoint was selected for each bootstrap sample, and these samples were classified with respect to CAD status; 4) the original data were then reclassified 200 times, using each set of parameters and the cutpoint estimated from the bootstrap samples. The biases of the resubstitution estimates of the misclassification rates were estimated by averaging the differences between the error rates found when classifying the original data and each bootstrap sample over the number of bootstrap samples.

To evaluate the performance of the best classification models for men and women as tools for screening general populations for CAD, Bayes’s theorem was applied to the sensitivities and specificities (after adjustment for bias) to obtain the post-test likelihood of disease conditional on the classification status assigned by the models. Because the post-test likelihood depends on disease prevalence in the screening population, plots were made of the post-test likelihood of having CAD given the screening outcome (with CAD or positive, no CAD or negative) versus disease prevalence.

Results

Means and standard deviations for continuous variables and distributions of dichotomous variables in patients with and without coronary disease are shown in Tables 1 and 2. Most variables tested bore a relation to CAD in one univariable analysis or another. The exceptions were body mass index (BMI), hemoglobin, uric acid, hypertension, and left ventricular hypertrophy. Total cholesterol and triglyceride were significantly related to CAD in all four age-sex groups; HDL, LDL, and cigarette smoking were each related to CAD in three of four age-sex groups. B-mode scores were significantly higher in coronary disease patients than controls for each of the four age-sex groups.

Logistic regression analysis was used to test whether the association between CAD and carotid atherosclerosis was confounded by an age effect. After correction for age by including it in the regression equation, the association between coronary and carotid atherosclerosis failed to reach statistical significance in men younger than 50 years, but persisted for all other groups \((p<0.001\) for women older than 50 years; \(p<0.003\) for women younger than 50 years; \(p<0.001\) for men older than 50 years; \(p<0.139\) for men younger than 50 years). Extent of carotid atherosclerosis also was correlated significantly \((p<0.05)\) with a number of other CAD risk factors in the univariable analysis in various age and sex categories. Age was significantly correlated with extent of extracranial carotid atherosclerosis in all four age and sex groups, whereas HDL, cigarette smoking, and plasma triglyceride concentration were significantly correlated in three of four, total cholesterol and LDL were significantly correlated in four of four, and hypertension, diabetes, family history, and left ventricular hypertrophy were significantly correlated in one of four groups, respectively.

Because a number of risk factors were significantly correlated with both coronary and carotid atherosclerosis, we next determined whether the relation between the atherosclerosis at these two sites was exclusively dependent on shared risk factors. First, a stepwise logistic regression analysis was used to identify those risk factors that were associated with presence or absence of coronary artery stenosis while simultaneously controlling for other risk factors. The results are shown in Table 3. When added to these models, B-mode score was found to have a statistically significant and independent relation to coronary status for men and women older than 50 years. For women older than 50, forcing the B-mode score into the model reduced coefficients of the age and smoking variables, making them nonsignificant. For men older than 50, entry of the B-mode score into the model reduced the coefficients for age and HDL, making them nonsignificant. B-Mode score was not independently associated with coronary stenosis in patients less than 50 years of age in the multivariable models (Table 3).

Because B-mode score was independently associated with CAD in individuals older than, but not in those younger than, 50 years, the next stage of analysis, evaluating the effect of B-mode score on our ability to classify subjects’ CAD status, was performed on men and women greater than 50 years of age only. Including B-mode score as an independent variable in the logistic models for men and women
TABLE 1. Univariable Analysis: Descriptive Data for Continuous Variables in Patients With or Without Coronary Artery Disease by Age-Sex Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women &gt;50 years old</th>
<th>Women ≤50 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With CAD (n=82)</td>
<td>Without CAD (n=60)</td>
</tr>
<tr>
<td>Age</td>
<td>63.2±7.0</td>
<td>59.9±5.7</td>
</tr>
<tr>
<td>TC</td>
<td>242.3±49.4</td>
<td>221.5±40.3</td>
</tr>
<tr>
<td>Log TG</td>
<td>2.3±0.2</td>
<td>2.1±0.2</td>
</tr>
<tr>
<td>HDL</td>
<td>41.3±9.7</td>
<td>47.8±12.9</td>
</tr>
<tr>
<td>LDL</td>
<td>162.6±43.9</td>
<td>148.8±30.6*</td>
</tr>
<tr>
<td>BMI</td>
<td>26.2±4.9</td>
<td>25.3±4.6</td>
</tr>
<tr>
<td>Pack-years</td>
<td>14.2±22.0</td>
<td>6.4±14.5*</td>
</tr>
<tr>
<td>Hgb</td>
<td>13.6±1.1</td>
<td>13.6±1.1</td>
</tr>
<tr>
<td>UA</td>
<td>6.2±1.6</td>
<td>6.1±1.7</td>
</tr>
<tr>
<td>B-mode</td>
<td>9.4±5.7</td>
<td>3.3±3.6</td>
</tr>
</tbody>
</table>

Values are mean±SD.
*p<0.05 for with CAD vs. without CAD groups; pt<0.01 for with CAD vs. without CAD groups.
TC, plasma concentration of total cholesterol; Log TG, logarithm of plasma triglyceride concentration; HDL, plasma concentration of high density lipoprotein cholesterol; LDL, plasma concentration of low density lipoprotein cholesterol; BMI, body mass index (wt/ht²); Hgb, serum hemoglobin concentration; UA, serum uric acid concentration; B mode, B mode score (index of extent of carotid atherosclerosis).

TABLE 2. Univariable Analysis: Descriptive Data for Dichotomous Variables in Patients With or Without Coronary Artery Disease by Age-Sex Groups: Percent With Attribute

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women &gt;50 years old</th>
<th>Women ≤50 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With CAD (n=82) (%)</td>
<td>Without CAD (n=60) (%)</td>
</tr>
<tr>
<td>High BP</td>
<td>72</td>
<td>57</td>
</tr>
<tr>
<td>With DM</td>
<td>23</td>
<td>7†</td>
</tr>
<tr>
<td>With FH</td>
<td>49</td>
<td>37</td>
</tr>
<tr>
<td>With LVH</td>
<td>20</td>
<td>8</td>
</tr>
</tbody>
</table>

Men >50 years old

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men ≤50 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With CAD (n=141) (%)</td>
</tr>
<tr>
<td>High BP</td>
<td>55</td>
</tr>
<tr>
<td>With DM</td>
<td>21</td>
</tr>
<tr>
<td>With FH</td>
<td>33</td>
</tr>
<tr>
<td>With LVH</td>
<td>12</td>
</tr>
</tbody>
</table>

BP, blood pressure status; DM, diabetes mellitus; FH, family history of coronary disease; LVH, left ventricular hypertrophy.
*p<0.05 for with CAD vs. without CAD groups (χ² test); pt<0.01 for with CAD vs. without CAD groups (χ² test).
TABLE 3. Logistic Regression Models for All Patients: B-mode Excluded From and Included in Models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women &gt;50</th>
<th>Women ≤50</th>
<th>Men &gt;50</th>
<th>Men ≤50</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-mode excluded from model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>-6.495</td>
<td>...</td>
<td>-5.891</td>
<td>...</td>
</tr>
<tr>
<td>Age</td>
<td>0.106</td>
<td>0.000</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>TC</td>
<td>0.010</td>
<td>0.018</td>
<td>0.023</td>
<td>0.000</td>
</tr>
<tr>
<td>HDL</td>
<td>-0.053</td>
<td>0.002</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Pack-year</td>
<td>0.025</td>
<td>0.028</td>
<td>0.056</td>
<td>0.001</td>
</tr>
<tr>
<td>DM</td>
<td>...</td>
<td>...</td>
<td>1.590</td>
<td>0.039</td>
</tr>
<tr>
<td>GOF p=0.081</td>
<td>GOF p=0.006</td>
<td>GOF p=0.550</td>
<td>GOF p=0.073</td>
<td></td>
</tr>
<tr>
<td>B-mode included in model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>-5.390</td>
<td>...</td>
<td>-5.730</td>
<td>...</td>
</tr>
<tr>
<td>Age</td>
<td>0.051</td>
<td>0.096</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>TC</td>
<td>0.010</td>
<td>0.035</td>
<td>0.022</td>
<td>0.000</td>
</tr>
<tr>
<td>HDL</td>
<td>-0.041</td>
<td>0.031</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Pack-year</td>
<td>0.017</td>
<td>0.207</td>
<td>0.054</td>
<td>0.002</td>
</tr>
<tr>
<td>DM</td>
<td>...</td>
<td>...</td>
<td>1.487</td>
<td>0.067</td>
</tr>
<tr>
<td>B-mode</td>
<td>0.248</td>
<td>0.000</td>
<td>0.052</td>
<td>0.609</td>
</tr>
<tr>
<td>GOF p=0.115</td>
<td>GOF p=0.057</td>
<td>GOF p=0.305</td>
<td>GOF p=0.079</td>
<td></td>
</tr>
</tbody>
</table>

LRC, logistic regression coefficient; TC, total plasma cholesterol concentration; HDLC, high density lipoprotein cholesterol concentration; Pack-year, pack-years of smoking; DM, diabetes mellitus; GOF p=p value for Hosmer-Lemeshow goodness of fit test.

Increased the sum of sensitivity and specificity for both groups. For women, the model without B-mode score had a sensitivity of 78% and a specificity of 75%, whereas these were 80% and 85%, respectively, for the model that included B-mode score. For men, the model without B-mode score had a sensitivity of 60% and specificity of 88%, compared with a sensitivity and specificity of 71% and 86%, respectively, for the model with B-mode. To determine the extent to which the addition of B-mode score to our roster of independent variables improved our ability to classify patients and controls, we constructed histograms of the predicted probabilities of correct classification (i.e., the predicted probabilities of being a case for cases and the predicted probabilities of being a control for controls) for models including and excluding B-mode (Figure 1). The Wilcoxon signed-rank test showed that the inclusion of B-mode score in the model resulted in significant increases in the median predicted probability of correct classification for both men (p<0.0001) and women (p<0.0001).

Although B-mode score showed a strong independent relation to CAD status in these equations and improved our ability to rank-order cases and controls by way of the predicted probabilities, our overall ability to dichotomize the group into CAD cases and disease-free controls was only significantly improved by adding the B-mode score to the model for men. For women, McNemar's test yielded a single degree of freedom χ² statistic of 2.21 (p=0.137); the corresponding test for men yielded a test statistic of 5.92 (p=0.015).

The results of patient classification using the recursive partitioning program CART were similar to logistic regression with respect to B-mode score. For both men and women when B-mode score was included as a candidate variable, it was the first variable on which subjects were split. For men without B-mode score in the classification tree, the data were split on LDL, HDL, age, pack-years of smoking, and total cholesterol. When B-mode score was included in the tree, the data were split on B-mode score and LDL (Figure 2). For women without B-mode score in the classification tree, the data were split on HDL, diabetes status, uric acid, and LDL. When B-mode score was included in the tree, it was the only variable on which data were split (Figure 3).

The relative importance rankings from CART implied that B-mode score was the most important individual classifier of CAD status. For women, the next-most-important variable, HDL, had a relative importance index of 70 on a scale of 0 to 100 (by definition B-mode score had a relative importance of 100 when compared with itself). For men, the next-most-important variable, total cholesterol, had a relative importance index of 67. In CART models for which B-mode score was not a candidate to enter, LDL and HDL were the most important variables for women and men, respectively. However, the relative importances of the next-most-important variables (body mass index for women and total cholesterol for men), compared with the most important variables in their respective trees, were 93 for both men and women. These results imply that B-mode score is, by far, the single most important classifier of CAD status for men and women older than 50 years and that its inclusion in the trees resulted in a reduction of the
Figure 1. Histograms of the predicted probabilities of correct classification for men and women older than 50 years, with and without B-mode score in the logistic models. Vertical axes show the number of subjects represented by the bars; horizontal axes show the interval midpoints. Note the right shift in the distributions for the models that include B-mode score.
Females $> 50$, B-mode Score Not a Candidate Variable

- Yes $142$
- No $46$
- Is HDL-C $\leq 48.5$?
- No $96$
- Yes $20$
- Is subject diabetic?
- No $78$
- Yes $76$
- Is uric acid $\leq 3.95$?
- No $29$
- Yes $71$
- Is LDL-C $\leq 141$?
- No $42$
- Yes $73$

Sensitivity $= .63$
Specificity $= .83$

Females $> 50$, B-mode Score is a Candidate Variable

- Yes $142$
- No $73$
- Is B-mode score $\leq 5.55$?
- No $42$
- Yes $71$
- Is LDL-C $\leq 141$?
- No $42$
- Yes $73$

Sensitivity $= .73$
Specificity $= .78$

**FIGURE 2.** Classification trees for women older than 50 years using CART. Circles are splitting points corresponding to the question beneath them; squares are terminal nodes, classification status is given beneath each node. Inside circles are the number of subjects eligible for the split; inside squares are the number of subjects classified in the node. Sensitivities and specificities for the classification rules are shown at the bottom of the trees.

Importance of other variables. These results are consistent with those of the logistic regression models.

Classification trees without B-mode score could be constructed that did not perform significantly worse than trees with B-mode score. The sensitivity and specificity for women when B-mode score was included in the model were 73% and 78%; when B-mode was not included, the sensitivity and specificity were 63% and 83%, respectively. For men, the sensitivity and specificity when B-mode was included were 72% and 86%, respectively; when B-mode was not included as a candidate for entry, the sensitivity and specificity were 82% and 77%, respectively. McNemar’s test indicated that trees with B-mode score did not classify patients significantly better than trees without B-mode score for men or women, yielding $\chi^2$ statistics of 0.47 ($p=0.493$) for women and 2.00 ($p=0.157$) for men.

Table 4 shows the sensitivities and specificities for both classification techniques and sex groups after adjusting for biases in the resubstitution estimates by cross-validation for the classification tree rules and bootstrap sampling for the logistic regression model rules. Estimated biases themselves are also presented. Comparing classification rules without B-mode to their counterparts with B-mode revealed that, generally, there was less bias in the rules with the B-mode score. Analysis of the specific differences in sensitivity and specificity for rules with and without B-mode score showed that biases for rules with B-mode score were smaller for each instance except one (for which they were equal). A Wilcoxon's
Males > 50, B-mode Score Not a Candidate Variable

Cases

Controls

Sensitivity = .82
Specificity = .77

Males > 50, B-mode Score Is a Candidate Variable

Cases

Controls

Sensitivity = .72
Specificity = .86

FIGURE 3. Classification trees for men older than 50 years using CART. Circles are splitting points corresponding to the question beneath them; squares are terminal nodes, classification status is given beneath each node. Inside circles are the number of subjects eligible for the split; inside squares are the number of subjects classified in the node. Sensitivities and specificities for the classification rules are shown at the bottom of the trees.

signed-rank test of these differences was significant ($p=0.008$), implying that there was less bias for rules that included B-mode score.

To ascertain the clinical usefulness of the model, we evaluated predictive values of positive and negative classification at all levels of CAD prevalence. Figure 4 shows the post-test likelihood of having CAD given the outcome of classification by the logistic regression models with B-mode score, separately for men and women.

Discussion

Population-based studies have identified relations between symptoms and signs of CAD and carotid artery disease. Patients with angina pectoris or myocardial infarction are more likely to experience stroke, as are patients with electrocardiographic abnormalities. Ischemic stroke has been found to develop in approximately 2–5% of patients in the first 1–2 weeks after myocardial infarction. Mechanisms whereby symptomatic manifestations of CAD
Table 4. Adjusted Sensitivities and Specificities for Men and Women Older Than 50 Years, Both Classification Techniques

<table>
<thead>
<tr>
<th>Model</th>
<th>Technique</th>
<th>Adjusted sensitivity (%)</th>
<th>Adjusted specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women &gt;50 yr</td>
<td>No B-mode</td>
<td>Logistic regression</td>
<td>74 (4)</td>
</tr>
<tr>
<td></td>
<td>Recursive partitioning</td>
<td></td>
<td>52 (11)</td>
</tr>
<tr>
<td></td>
<td>With B-mode</td>
<td>Logistic regression</td>
<td>77 (3)</td>
</tr>
<tr>
<td></td>
<td>Recursive partitioning</td>
<td></td>
<td>76 (–3)</td>
</tr>
<tr>
<td>Men &gt;50 yr</td>
<td>No B-mode</td>
<td>Logistic regression</td>
<td>54 (6)</td>
</tr>
<tr>
<td></td>
<td>Recursive partitioning</td>
<td></td>
<td>70 (12)</td>
</tr>
<tr>
<td></td>
<td>With B-mode</td>
<td>Logistic regression</td>
<td>69 (3)</td>
</tr>
<tr>
<td></td>
<td>Recursive partitioning</td>
<td></td>
<td>70 (1)</td>
</tr>
</tbody>
</table>

Entries in parentheses are estimated percent biases in resubstitution estimates (i.e., resubstitution sensitivity or specificity minus adjusted sensitivity or specificity).

lead to cerebrovascular symptoms include arrhythmia, heart failure, and embolus from left ventricular thrombus, in isolation or after myocardial infarction. In addition, clinical studies of patients undergoing cardiovascular surgery have shown that 10–20% have positive carotid Doppler exams. Although these studies define symptomatic heart disease as an important precursor of cerebrovascular symptoms, signs and symptoms of cerebrovascular disease are also important precursors of complaints that relate to the heart: patients with transient ischemic attacks, asymptomatic bruit, and stroke die of myocardial infarction more often than of cerebrovascular disease. Studies have also shown that 30–60% of symptomatic patients with transient ischemic attacks, asymptomatic carotid bruits, and stroke have positive treadmill tests or angiographic evidence of CAD.

The interrelations between symptoms attributable to the coronary and carotid arteries suggested above might reflect common risk factors. Older individuals are, for instance, more likely to have both cerebrovascular disease and CAD. A number of studies have shown similarities between risk factors for symptomatic CAD and cerebrovascular disease. However, differences have also been noted: lesser sex differential for stroke, lesser effect of cholesterol on stroke, more profound effect of hypertension as a precursor of stroke, and geographic differences in stroke and heart attack event rates.

A recent review has examined the information gained from studies of the relation between risk factors and atherosclerosis of the coronary arteries. Of necessity, such studies are based on samples of patients undergoing coronary angiography because there is no accurate means to measure disease of the coronary arteries noninvasively and because the relation of symptoms to atherosclerosis in this arterial bed is notoriously poor. Because of the nature of the patient selection process, these studies can only provide suggestive evidence for links between various patient attributes and coronary status; however, in general, studies using such patients have yielded data consistent with other epidemiological studies. Investigators have identified age, sex, LDL and HDL, blood pressure, cigarette smoking, and diabetes as the most consistently important risk factors for symptomatic CAD. For cerebrovascular disease, our own studies have identified age, hypertension, cigarette smoking, HDL, race, uric acid, and left ventricular hypertrophy as important risk factors. LDL was also independently related to extent of extracranial carotid atherosclerosis in patients with CAD. Recently, Salonen et al identified age, cigarette smoking, and LDL as risk factors for extracranial carotid atherosclerosis in a randomly chosen male population-based sample.

In the current study, CAD-free controls had less extensive carotid atherosclerosis than CAD cases in each of four age and sex groups. This observation is consistent with published autopsy studies that have shown Pearson correlations between carotid and coronary atherosclerosis of r=0.45. In the present study, the relation persisted, after controlling for age, in men and women older than 50 and in women younger than 50 years, but not in men younger than 50 years.

Figure 4. Post-test likelihood of having coronary artery disease (CAD) given outcome of screening for disease using logistic regression models including B-mode score versus CAD prevalence for men and women older than 50 years. Downwardly concave lines [labeled "TEST (+)"] correspond to the projected post-test likelihoods of CAD given a positive classification separately for women (solid line) and men (broken line). Upwardly concave lines [labeled "TEST (-)"] give the projected likelihood of having CAD given that the screening outcome was negative separately for women (solid line) and men (broken line).
Several of the risk factors that persisted in multivariable analyses (notably age, HDL, and pack-years of smoking) were identical to those identified previously as risk factors for carotid atherosclerosis.\textsuperscript{14,15} Of interest, high blood pressure, which was strongly related to extent of extracranial carotid atherosclerosis in multivariable analyses,\textsuperscript{14} was unrelated to coronary status. For men and women older than 50 years, forcing extent of extracranial carotid atherosclerosis into the multivariate models as a candidate independent variable resulted in loss of statistical significance of age and pack-years of smoking for women, and age and HDL for men. Reduction of the significance of these variables reflects the previously demonstrated association of the established risk factors for coronary atherosclerosis (e.g., cholesterol levels, smoking) with carotid atherosclerosis and, perhaps, the ability of B-mode score to measure some additional (possibly as yet unknown) risk factors for CAD that were not measured directly in this study.\textsuperscript{14,15} It is additionally important to stress the obligatory imprecision of measurements of risk factors in a case control study such as this one. Risk factors (e.g., hypertension) are measured at a single point in time and may have been controlled, to varying degrees, many years before the study. Duration of exposure to certain risk factors cannot be defined precisely. Finally, interactions between certain risk factors may dictate that their combined effect is the product rather than the sum of their individual effects. Because carotid and coronary atherosclerosis share a certain number of these risk factors, disease of the carotid arteries may serve as a "time-integrated" index that better identifies risk factor exposure and interrelations of risk factor exposures than does the individual measurement of the risk factor itself. Use of the classification rule including B-mode score to predict disease status in individuals older than 50 years at various levels of disease prevalence is pictorially represented in Figure 4. For disease prevalences between 20% and 80%, using the logistic models with B-mode score to screen for CAD contributes a considerable amount of information regarding CAD status. For example, in a population with 40% prevalence of CAD (assuming equivalent disease prevalences for women and men), it is projected that a negative classification by the logistic model would reduce a randomly selected women’s likelihood of having disease from 60% to about 17%, and a randomly selected men’s likelihood of having disease given a negative screening result would be about 20%. Conversely, if the result of the logistic classification were positive for a randomly selected woman, it is projected that her likelihood of having CAD would increase from 40% to about 74%, and for a randomly selected man with a positive classification, the likelihood of having CAD would be about 68%.

When B-mode was tested as a candidate independent variable in multivariable analysis for men and women younger than 50, it was nonsignificant. The similarities of the univariate relations between extracranial carotid atherosclerosis and coronary status in older and younger individuals shown in Table 1 suggest that, at least partly because extent of atherosclerosis is reduced, overall, in the younger samples, power to detect differences between cases and controls younger than 50 may be reduced.

Because the B-mode score appeared as an independent variable in logistic regression models for patients older than 50, we next asked whether extent of carotid atherosclerosis would aid in classification of their coronary status. This approach may be compared with our previous analyses in which we evaluated coronary status as an independent variable and measured its association with extent of extracranial carotid atherosclerosis.\textsuperscript{14,15} In those studies, we found that coronary status was an independent predictor of extent of carotid atherosclerosis and that classification of patients according to presence or absence of CAD enabled us to account for an additional 5% of the variability in extracranial carotid atherosclerosis when that term was added to a model that included other risk factors. In the current studies, we were similarly able to demonstrate an independent effect of B-mode score to classify CAD status. Inclusion of B-mode score as an independent variable generally resulted in a significant increase in the median predicted probability of correct classification for both sex groups (Figure 1). However, this improvement was only statistically significant for men older than 50 years (logistic regression, McNemar’s test). In this regard, there is a well-recognized tendency for symptomatic cerebrovascular disease to “lag” 10 to 15 years behind CAD.\textsuperscript{54} It is not known whether cerebrovascular and cardiovascular atherosclerosis show a similar temporal separation. The present data suggest that extent of carotid atherosclerosis shows a consistent and significant relation to coronary artery disease in men and women older than and younger than 50 years (univariable analysis), that the relation is independent of other variables in men and women older than 50 years, and that coexistence of disease in the coronary and carotid arteries cannot entirely be explained by shared risk factors that were measured in this study. The possibility exists that other shared risk factors not measured in this study partly explain the association between atherosclerosis of the carotid and coronary arteries or that arterial wall factors are involved.\textsuperscript{14,15}

Alternatively, carotid atherosclerosis may serve as a proxy for the time-integrated effect of certain risk factors or interactions between risk factors.

Furthermore, the results we have presented provide evidence that a measure of the degree of carotid artery atherosclerosis is at least as useful as other known risk factors to screen for CAD. It is easy to implement the logistic regression approaches in the spreadsheet program on a microcomputer, allowing their clinical use. The results are consistent with observations made by Criqui et al.,\textsuperscript{55} who have used noninvasive methods to quantify disease of the arteries of the lower extremities and relate peripheral vascular disease to all-cause mortality. This evidence
provides rationale for research that investigates the ability of measures of peripheral vascular diseases (carotid and lower extremity) to identify potential CAD patients in a population-based sample. Outcomes regarding coronary heart and other cardiovascular disease in relation to carotid status are currently being evaluated in two NIH-funded multi-center population-based cohort studies—the Atherosclerosis Risk in Communities (ARIC) study56 and the Cardiovascular Health Study (CHS). Results from these community-based studies, our own hospital-based studies, and those of others55 will identify the role of noninvasive evaluations of peripheral arteries in the identification of patients with CAD.

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