An Algorithm for Noninvasive Identification of Angiographic Three-Vessel and/or Left Main Coronary Artery Disease in Symptomatic Patients on the Basis of Cardiac Risk and Electron-Beam Computed Tomographic Calcium Scores

Axel Schmermund, MD,* Kent R. Bailey, PhD,† John A. Rumberger, PhD, MD, FACC,* Judd E. Reed, BS,‡ Patrick F. Sheedy II, MD,§ Robert S. Schwartz, MD, FACC*

Rochester, Minnesota

OBJECTIVES

We sought to model an algorithm for noninvasive identification of angiographically obstructive three-vessel and/or left main disease based on conventional cardiac risk assessment and site and extent of coronary calcium determined by electron-beam computed tomography (EBCT).

BACKGROUND

Such an algorithm would greatly facilitate clinical triage in symptomatic patients with no previous diagnosis of coronary artery disease (CAD).

METHODS

We examined 291 patients with suspected, but not previously diagnosed, CAD who underwent coronary angiography for clinical indications. Cardiac risk factors were determined as defined by the National Cholesterol Education Program. An EBCT scan was performed in all patients, and a coronary calcium score (Agatston method) was computed. Total per-patient calcium scores and separate scores for the major coronary arteries were generated. These scores were also analyzed for localization of coronary calcium in the more distal versus proximal tomographic sections. These parameters and the risk factors were considered for the model described in the following section.

RESULTS

Sixty-eight patients (23%) had angiographic three-vessel and/or left main CAD. Multiple logistic regression analysis determined male sex, presence of diabetes and left anterior descending (LAD) and circumflex (LCx) coronary calcium scores, independent from more distal calcium localization, as independent predictors for identification of three-vessel and/or left main CAD. Based on this four variable model, a simple noninvasive index (NI) was constructed as the following: \( \log_e(\text{LAD score}) + \log_e(\text{LCx score}) + 2[\text{if diabetic}] + 3[\text{if male}] \). Receiver operating characteristic curve analysis for this NI yielded an area under the curve of 0.88 ± 0.03 (p < 0.0001) for separating patients with, versus without, angiographic three-vessel and/or left main CAD. Various NI cutpoints demonstrated sensitivities from 87–97% and specificities from 46–74%. The NI values >14 increased the probability of angiographic three-vessel and/or left main CAD from 23% (pretest) to 65–100% (posttest), and NI values <10 increased the probability of no three-vessel and/or left main CAD from 77% (pretest) to 95–100% (posttest).

CONCLUSIONS

On the basis of a simple algorithm ("noninvasive index"), EBCT calcium scanning in conjunction with risk factor analysis can rule in or rule out angiographically severe disease, i.e., three-vessel and/or left main CAD, in symptomatic patients. (J Am Coll Cardiol 1999;33:444–52) © 1999 by the American College of Cardiology

The identification of symptomatic patients with angiographic three-vessel and/or left main coronary artery disease (CAD) is becoming increasingly important. These patients are at high risk (1–3) and usually require coronary angiography and consideration for revascularization, whereas further noninvasive evaluation and risk stratification may be justified for patients with less severe CAD (4).

Coronary risk factors do not allow individual discrimination of severity of angiographic CAD (5,6) or adverse outcomes (7), but are useful prognostic indicators in large patient populations. However, for triage of patients who may require coronary catheterization, one also relies on more direct measures of the extent and severity of CAD as
Abbreviations and Acronyms

CAD = coronary artery disease
CASS = Coronary Artery Surgery Study
CT = computed tomography
EBCT = electron-beam computed tomography
HDL = high-density lipoprotein
LAD = left anterior descending coronary artery
LCx = left circumflex coronary artery
LDL = low-density lipoprotein
NI = noninvasive index
ROC = receiver operating characteristic

can be provided by stress echocardiography (8,9) or radionuclide perfusion imaging (10,11).

As opposed to other noninvasive cardiac imaging modalities focusing on the physiological consequences of coronary obstruction, coronary calcium quantified by electron-beam computed tomography (EBCT) represents anatomic disease itself, i.e., coronary plaque burdens (12,13). Coronary calcium predicts the presence (14,15) and extent (16) of obstructive angiographic CAD, and the amounts of detectable calcified plaque can be used to estimate the likely severity of maximum angiographic stenosis (17). However, depending on a patient’s risk profile, consideration of coronary calcium alone for estimation of coronary disease can be misleading in some cases (18,19). Combination of risk factor assessment and EBCT should be superior to either method alone for the identification of angiographic three-vessel and/or left main disease, but this has not been previously explored. We therefore sought to model a clinically applicable noninvasive index based on the analysis of conventional cardiac risk factors as defined by the National Cholesterol Education Program (NCEP) (20) and EBCT-derived quantity of coronary calcium.

METHODS

Patients. The research protocol was approved by the Mayo Clinic Institutional Review Board. Consecutive patients who underwent diagnostic coronary angiography for clinical indications were invited to participate in the research protocol if they had no previous arteriographic documentation of CAD, coronary artery bypass surgery or previous cardiac transplant surgery. Also, no patient had unstable angina or underwent angioplasty at the time of initial angiography. After signed informed consent, EBCT scanning was performed on an average of one day following arteriography. Results from subsets of this patient population have been published previously (14,17,21,22). On the basis of a clinical diagnosis of previous myocardial infarction or signs of ischemia in the resting electrocardiogram, 31 patients with known CAD before admission were excluded to obtain a more homogeneous sample. In the remaining 291 patients, the most common indication for coronary angiography was chest pain (typical or atypical angina) in 205 patients (71%). Thirty nine patients (13%) had abnormal conventional stress tests, 21 (7%) had unexplained exertional dyspnea, 19 (7%) were examined preoperatively (usually for valvular heart disease), six (2%) had congestive heart failure, and 1 was examined for a disability claim.

Coronary angiography. Coronary angiography was performed by the Judkins technique with a minimum of five views of the left system and two views of the right system. The angiograms were analyzed according to the coronary segmental classification proposed by the Coronary Artery Surgery Study (CASS) investigators (5). The maximum percent diameter stenosis in any of the 27 coronary segments was visually assessed by two experienced angiographers who were unaware of the results of EBCT. Segments were defined as containing no or nonobstructive stenoses (0% to <50% luminal diameter narrowing), or stenoses from 50% to 100% (obstructive disease). This allowed classification of patients according to the presence or absence of obstructive three-vessel and/or left main disease. In case of a disagreement in the interpretation of a given angiogram, it was arbitrated with the help of a third angiographer as described previously (17).

Cardiac risk factors. We used the current NCEP definitions for cardiac risk factors (20), taking into account age and gender, family history of coronary artery disease, current cigarette smoking, hypertension (systolic and/or diastolic blood pressure values \( \geq 140 \) mmHg and \( \geq 90 \) mmHg, respectively, antihypertensive treatment, or both), diabetes mellitus and total and high-density lipoprotein (HDL)-cholesterol. Analysis of fasting total cholesterol and triglycerides was performed in 260 patients with EBCT. No patients were taking lipid-lowering medications at the time of study-entry. HDL-cholesterol was determined in 236 patients with EBCT, in whom the ratio of total/HDL-cholesterol was computed.

Electron-beam computed tomography. High resolution, noncontrast enhanced EBCT examinations (Imatron C-100 scanner, Imatron Inc., South San Francisco, California) were performed in a manner described previously (14,17). In all subjects, 40 contiguous, 3 mm thick, transaxial images were done commencing at the root of the aorta and proceeding caudad through the apex of the heart. For each study, a calcium score was determined using the methods of Agatston and colleagues (23). This algorithm has been widely used in research and clinical studies (12–14,16,17,21,22). The calcium score is the product of the area of coronary artery calcium (at least two contiguous pixels with a computed tomography (CT) density \( \geq 130 \) Hounsfield Units) and a factor rated 1–4 dictated by the maximum CT density within that lesion. A calcium score was calculated for each of the major coronary arteries (left main, left anterior descending, left circumflex and right coronary arteries) and the entire epicardial coronary system ("total calcium score"). In addition, the calcium score per
tomographic level was computed as a measure of the distribution of coronary calcium from proximal (base of the heart) to distal (apex). All EBCT analyses were performed without knowledge of the angiographic CAD severity.

**Statistics.** Statistical analyses were performed using the SPSS (versions 6.1.4 and 8.0, SPSS Inc., Chicago, Illinois) and SAS (version 6.08, SAS Institute, Cary, Indiana) software packages. Values are reported as mean ± SD unless otherwise indicated. Consistent with previous reports (14–17, 22–24), total calcium scores in the present study comprised a great range of values (0 through 7,633), but were mostly well below 1,000, with the 75th percentile at 545. To minimize the statistical influence of extreme values, all calcium score values were transformed to the natural logarithmic scale (24). Independent predictors of the presence of angiographic three-vessel and/or left main disease were determined by multiple logistic regression analysis. On the basis of this analysis, a “noninvasive index” (NI) of severe angiographic CAD was generated, according to the coefficients of the independent predictors. These coefficients can be interpreted as indicating the relative weight of the predictors with respect to the dependent variable. The NI was dichotomized at 10 equally spaced cutpoints for tabulation of sensitivity and specificity and related measures, whereas for all other calculations, the complete range of the NI was used. The standard errors for sensitivity and specificity were determined as described by Diamond and Forrester (25). Receiver operating characteristic (ROC) curve analysis was generated to test the predictive discrimination of patients with or without three-vessel and/or left main CAD. To analyze the predictive discrimination of the NI compared with either only risk factor variables or only EBCT-derived calcium score variables, the areas under these ROC curves were generated and tested for significant differences (26). The ROC curves were derived from multiple logistic regression analyses. These analyses identified independent risk factor or calcium score predictors based only on all risk factor or all calcium score variables, respectively. The predicted values from these analyses represented the aggregate predictive information of the model and were entered into the ROC curve analysis.

Finally, to analyze the predictive value of a positive or negative result at each NI cutpoint, probability ratios were computed on the basis of positive and negative likelihood ratios (27). The positive likelihood ratio (+)LR was defined as follows:

\[
(+)LR = \frac{\text{Sensitivity}}{1 - \text{Specificity}}
\]  

[1]

The negative likelihood ratio (−)LR was defined as follows:

\[
(-)LR = \frac{\text{Specificity}}{1 - \text{Sensitivity}}
\]  

[2]

A positive or negative test result was defined as a value of the NI above or below specific cutpoints. According to Bayes’ theorem (27), the posttest probability of (severe angiographic) disease after a positive test result was defined as follows:

\[
(+)\text{PTPD} = \frac{\text{PPD}}{\text{PPD} + \text{PPN}(+)\text{LR}} \times 100
\]  

[3]

(+)PTPN means “posttest probability of disease after a positive test result,” PPD mean “pretest probability of disease,” and PPN means “pretest probability of no disease.” The posttest probability of no (severe angiographic) disease after a negative test result was defined as follows:

\[
(-)\text{PTPN} = \frac{\text{PPN}}{\text{PPN} + \text{PPD}(-)\text{LR}} \times 100
\]  

[4]

(−)PTPN means “posttest probability of no disease after a negative test result.” The pretest probabilities of disease and no disease, referring to angiographic three-vessel and/or left main CAD, were estimated empirically, i.e., on the basis of the actual angiographic findings in our patients. As is explained in more detail in the following section, the prevalence of three-vessel and/or left main CAD in our patients was very comparable to that found in the CASS registry with 24,595 patients (2), and thus seemed to offer a reasonable estimate.

For all statistical evaluations, a 2-tailed p-value <0.05 was considered significant.

**RESULTS**

**Patient demographics.** Of the 291 patients, 68 (23%) had angiographically significant three-vessel and/or left main disease. Risk factors are listed in Table 1. Table 2 gives EBCT total calcium scores and calcium scores separately for the major coronary arteries. Twenty seven patients (9%) had no coronary calcium detected by EBCT, 38 (13%) had calcium in one of the major coronary arteries, 62 (21%) in 2, 111 (38%) in 3, and 53 (18%) in all four. In the left coronary system (left main, left anterior and left circumflex coronary arteries), 90% of all calcified lesions were detected in the 14 more proximal (vs. 26 more distal) levels, and 98% in the 20 more proximal (vs. 20 more distal) levels. In the right coronary artery, 90% of all calcified lesions were detected in the 30 more proximal (vs. 10 more distal) levels, and 98% in the 36 more proximal (vs. 4 more distal) levels.

**Predicting angiographic three-vessel and/or left main disease.** Multivariate logistic regression analysis identified male sex, diabetes mellitus, age, and, with borderline significance (p = 0.06), family history as independent risk factor predictors of angiographic three-vessel and/or left main disease. Total cholesterol values or, alternatively, the ratio of total/HDL-cholesterol, and calculated LDL-cholesterol levels did not remain in the model. This was also true for smoking and systemic hypertension. Considering only EBCT-derived variables, coronary calcium scores separately generated for the left circumflex and left anterior descending coronary arteries (LAD) were independent predictors. Figure 1 shows that left circumflex (LCx) coronary calcium scores enabled the best separation between patients...
Table 1. Cardiac Risk Factor Characteristics of the Patients With Angiographic Three-Vessel and/or Left Main Disease and of the Overall Patient Sample

<table>
<thead>
<tr>
<th>Risk Factor Variables</th>
<th>Angiographic Three-Vessel and/or Left Main Disease (n = 68)</th>
<th>No angiographic Three-Vessel and/or Left Main Disease (n = 223)</th>
<th>All Patients (n = 291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 10*</td>
<td>54 ± 11</td>
<td>56 ± 11</td>
</tr>
<tr>
<td>Male sex (number [%])</td>
<td>62 [91]*</td>
<td>165 [74]</td>
<td>227 [78]</td>
</tr>
<tr>
<td>Present smoking (number [%])</td>
<td>11 [16]</td>
<td>59 [27]</td>
<td>70 [24]</td>
</tr>
<tr>
<td>Diabetes (number [%])</td>
<td>15 [22]*</td>
<td>27 [12]</td>
<td>42 [14]</td>
</tr>
<tr>
<td>Family history (number [%])</td>
<td>41 [60]</td>
<td>107 [48]</td>
<td>148 [51]</td>
</tr>
<tr>
<td>Systemic hypertension (number [%])</td>
<td>37 [54]</td>
<td>94 [42]</td>
<td>131 [45]</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>221 ± 37</td>
<td>219 ± 53</td>
<td>219 ± 50</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>43 ± 13</td>
<td>43 ± 15</td>
<td>43 ± 15</td>
</tr>
<tr>
<td>Total/HDL-cholesterol</td>
<td>5.6 ± 1.9</td>
<td>5.5 ± 1.9</td>
<td>5.5 ± 1.9</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>163 ± 94</td>
<td>194 ± 14</td>
<td>187 ± 139</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. No angiographic three-vessel and/or left main disease. HDL = high-density lipoprotein.

Table 2. EBCT Characteristics (Log$_e$-Transformed Scores) of the Patients With Angiographic Three-vessel and/or Left Main Disease and of the Overall Patient Sample

<table>
<thead>
<tr>
<th>Calcium Score Variables</th>
<th>Angiographic Three-vessel and/or Left Main Disease (n = 68)</th>
<th>No Angiographic Three-vessel and/or Left Main Disease (n = 223)</th>
<th>All Patients (n = 291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total calcium score</td>
<td>6.3 ± 1.5* [6.6; 5.8, 7.3]</td>
<td>3.7 ± 2.4 [4.1; 5.1, 5.8]</td>
<td>4.3 ± 2.5 [5.0; 2.1, 6.3]</td>
</tr>
<tr>
<td>LM score</td>
<td>1.0 ± 1.7* [0.0; 0.0, 0.0]</td>
<td>0.5 ± 1.2 [0.0; 0.0, 0.0]</td>
<td>0.6 ± 1.3 [0.0; 0.0, 0.0]</td>
</tr>
<tr>
<td>LAD score</td>
<td>5.5 ± 1.5* [5.9; 4.7, 6.5]</td>
<td>2.9 ± 2.4 [2.8; 0.0, 5.0]</td>
<td>3.5 ± 2.4 [4.2; 0.8, 5.6]</td>
</tr>
<tr>
<td>LCx score</td>
<td>4.4 ± 1.9* [4.8; 3.5, 5.6]</td>
<td>1.7 ± 1.9 [0.9; 0.0, 3.3]</td>
<td>2.3 ± 2.2 [1.7; 0.0, 4.4]</td>
</tr>
<tr>
<td>RCA score</td>
<td>4.7 ± 2.2* [5.2; 3.3, 6.3]</td>
<td>2.1 ± 2.1 [1.5; 0.0, 3.8]</td>
<td>2.7 ± 2.4 [2.2; 0.4, 4.9]</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. No angiographic three-vessel and/or left main disease. LAD = left anterior descending coronary artery, LM = left main stem, LCx = left circumflex coronary artery, RCA = right coronary artery.
NI represented the aggregate information for predicting the probability of angiographic three-vessel and/or left main coronary artery disease.

Noninvasive Index =

\[ \log_e(LAD) + \log_e(LCx) + 2[\text{if diabetic}] + 3[\text{if male}] \]

"\( \log_e(LAD) \)" and "\( \log_e(LCx) \)" are separate calcium scores for the LAD and (LCx), respectively, transformed to the natural logarithmic scale. The NI ranged from 0 through 20.32 in our patients. Figure 2 shows that using ROC characteristic analysis, the NI yielded an area under the curve (AUC) of 0.88 ± 0.03 (±SEM) for separation of patients with versus without angiographic three-vessel and/or left main disease. This was a significantly better predictive discrimination than risk factors alone (AUC = 0.77 ± 0.04, p-value for difference = 0.002) and an apparent trend compared with EBCT-derived variables alone (AUC = 0.86 ± 0.03, p-value for difference = 0.051). All three curves shown in Figure 2 were significantly different from a random distribution, i.e., an AUC of 0.5.

**Sensitivity and specificity analyses.** Using the NI, a cutpoint of 11.20 yielded a sensitivity of 82 ± 5% (±SEM, 56 of 68 patients with severe angiographic disease correctly classified), a specificity of 80 ± 3% (162 of 223 patients without severe angiographic disease correctly classified), a positive predictive value of 56 ± 3%, and a negative predictive value of 94 ± 3%. From a clinical and screening perspective, a model with a high sensitivity rather than specificity, and accordingly high negative predictive values, would be desirable (26). To give an overview of how the NI might be interpreted clinically, it was categorized into 10 cells so that a score of 0 through 2 was "1"; 2 through 4 was "2"; and so forth, with scores ≥18 being "10" (Table 4). With higher categories of the NI, more patients had severe angiographic disease (p < 0.0001, χ² test). Depending on different cutpoints of the categorized NI, varying sensitivities and specificities for the prediction of severe angiographic disease were generated, as demonstrated in Table 4. For example, choosing as cutpoint a categorized NI of 3, sensitivity was 97 ± 2%, and specificity was 46 ± 3%. At this same cutpoint, positive and negative likelihood ratios were 1.80 and 15.33, respectively, indicating high posttest odds of no disease relative to the pretest estimate of no disease and thus an increased rule-out power (27). A cutpoint of 7, on the other hand, was associated with a sensitivity of 40 ± 6% and a specificity of 96 ± 1%. Positive and negative likelihood ratios were 8.85 and 1.60, respectively, indicating an increased rule-in power at this cutpoint.

Posttest probabilities of disease or no disease after a positive or negative test result, respectively, are shown in Table 4 and Figure 3. Posttest probabilities of disease could not be calculated at the extreme ends of the NI-range, because sensitivities and specificities regarding the detection

---

**Table 3. Independent Predictors of Angiographic Three-Vessel and/or Left Main Disease**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>chi-Square</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Sex</td>
<td>1.47</td>
<td>0.58</td>
<td>6.46</td>
<td>0.011</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1.11</td>
<td>0.50</td>
<td>4.93</td>
<td>0.026</td>
</tr>
<tr>
<td>LCx Calcium Score</td>
<td>0.42</td>
<td>0.11</td>
<td>16.28</td>
<td>0.0001</td>
</tr>
<tr>
<td>LAD Calcium Score</td>
<td>0.40</td>
<td>0.12</td>
<td>10.49</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.

Multivariate logistic regression analysis in 291 patients. The coefficient of the intercept was −2.74 ± 0.81.
of angiographic three-vessel and/or left main CAD were 100%. On the basis of the actual angiographic findings, the pretest probability of (severe angiographic) disease was 23% in our patients (solid line in Figure 3a). From Table 4 and Figure 3, it can be appreciated that relative to the pretest value, the posttest probability of disease increased with greater NI cutpoint values. Relative to the pretest probability of no disease, i.e., 77%, the posttest probability of no disease increased with smaller NI cutpoint values. Figure 3a shows that a relatively high NI in the range above 14 increased the probability of disease to above 65% (arrow). As shown in Figure 3b, a relatively low NI of less than 10 increased the probability of no disease to above 95% (arrow). Most patients, 209 of 291 (72%), had NI values >14 or <10.

**DISCUSSION**

In the present investigation, only patients with suspected, but not previously known, CAD and no diagnostic signs of ischemia on the resting electrocardiogram were examined. Our results demonstrate that in these patients, noncontrast EBCT calcium scanning in conjunction with risk factor analysis can be used to noninvasively identify angiographic three-vessel and/or left main CAD. We constructed a simple algorithm, the NI, on the basis of the independent predictors of angiographic three-vessel and/or left main CAD in our patients, i.e., male sex, diabetes, and left anterior descending and circumflex coronary calcium scores (Table 3). Using cutpoints of this NI ranging from 4 through 10, sensitivities on the order of 87–97% and specificities on the order of 46–73% were generated (Table 4). On the basis of the actual prevalence of severe disease in
atic patients who probably should be sent for angiography.

Our patients, i.e., angiographic three-vessel and/or left main CAD, high NI values >14 increased the probability of severe disease from 23% to >65%, and low NI values <10 increased the probability of no severe disease from 77% to >95% (Fig. 3). Most patients (72%) had NI values in this range. No patients with an NI ≤ 4.98 (n = 86) and 30 of 42 patients (71%) with an NI ≥ 13.75 had angiographic three-vessel and/or left main CAD. Therefore, the NI as developed has potential to be useful in selecting symptomatic patients who probably should be sent for angiography (high NI) versus those who probably should have further noninvasive stratification (low NI).

**Patient demographics.** The prevalence in the current investigation of 23% of patients with angiographic three-vessel and/or left main CAD was comparable to that of 28% in 24,595 patients enrolled in the CASS (2) (p = 0.085). Total cholesterol levels were somewhat lower than reported in the early 1980s in CASS patients (5) and other, independent symptomatic patient cohorts (28), but were comparable to more recent reports (29,30). Also, the prevalence of the nonlipid risk factors was very similar to that in these recent reports (29,30) with the exception of less active smokers among our patients. This cohort thus seems fairly representative of symptomatic patients currently referred for coronary angiography.

**Combination of EBCT and risk factors.** The NI was clearly a superior discriminator of patients with versus without severe disease compared with use of the risk factors measured in our study alone (Fig. 2), but the enhanced discrimination compared with the use of EBCT-derived calcium scores alone did not quite reach significance (p = 0.051). Although it is possible that the association of calcium score values with angiographic three-vessel and/or left main CAD is indeed so strong that the role for risk factor predictors is diminished, one should keep in mind that the sample size of the current investigation was comparably small. Obviously, clinical decisions should not rely on a single test such as EBCT, and future studies with larger populations may well demonstrate a greater relative importance of risk factor variables. Also, the newer hemostatic and inflammatory risk factors such as fibrinogen and C-reactive protein (31) were not available. Cardiovascular risk factor exposure varies considerably across populations, dictated by cultural, geographic, and ethnic attributes, among other factors (32). It is therefore conceivable that risk factors other than those determined by the present investigation predict angiographic three-vessel and/or left main CAD in other patient cohorts. An interesting observation was that, although lipids are important factors in the development of atherosclerosis, they were of little value for separating degrees of severity of angiographic CAD in our regression model. This is consistent with previous reports released by us (in an independent patient population) (24) and others (5,28,30) stating that lipid risk factors are better discriminators of the presence or absence, rather than the severity of, coronary atherosclerotic disease.

**EBCT and coronary angiography.** In our opinion, the EBCT-derived predictors of severe angiographic disease identified in this investigation can be expected to be similar across various patient populations. Coronary calcium is representative of underlying coronary atherosclerotic plaque and plaque burden (12,13,33) and should thus have relatively continuous associations with atherosclerotic disease severity. It was not surprising that separate calcium scores...
generated for the left circumflex and left anterior coronary arteries remained in the regression model, whereas total calcium scores did not. Statistically, generation of a total score out of several per-vessel scores leads to a loss of information. In addition, coronary atherosclerosis, and coronary calcification, appears first in the proximal portions of the LAD (13,34). Coronary calcification is observed comparably late in the atherosclerotic disease process in the left circumflex coronary artery (13,34,35). Thus, defining the quantities of calcified plaques in the LAD is more sensitive for the detection of severe angiographic disease, whereas defining the quantities of calcified plaques in the LCx is more specific.

The interpretation of coronary angiograms in the current study was subject to the considerable intra- and interobserver variability reported in previous studies (36). However, the probability of systemic errors was low, because the angiograms were prospectively interpreted based on the agreement of two experienced, blinded angiographers. Intra- and interobserver variability of EBCT calcium scores has been reported to be negligible (37).

Conclusions. We have proposed a NI for the identification of severe angiographic CAD in symptomatic patients. This index, derived from a specific initial patient cohort, seems to be useful for establishing a high (65–100%) as opposed to a low (0–5%) probability of angiographic three-vessel and/or left main disease in most patients. It may thus facilitate individual decision-making concerning the urgency of coronary catheterization in symptomatic patients. However, this needs to be confirmed in a much larger prospective study design.

Acknowledgment
We thank Robert L. Frye, MD, for initially posing the important clinical question regarding the detection of three-vessel and/or left main disease and focusing our attention on this topic.

Reprint requests and correspondence: Dr. Axel Schmermund, Department of Cardiology, University Clinic Essen, Hufelandstrasse 55 D-45122 Essen, Germany Email: Axel.Schmermund@uni-essen.de.

References
20. National Cholesterol Education Program. Second report of the expert panel on detection, evaluation, and treatment of


