Measuring the Effect of Risk Factors on Coronary Atherosclerosis: Coronary Calcium Score Versus Angiographic Disease Severity

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Objectives. This study sought to determine whether noninvasive quantification of coronary calcium is comparable to selective coronary angiography in measuring the effect of cardiovascular risk factors on coronary atherosclerosis.

Background. Electron beam computed tomography (EBCT) allows the delineation of anatomic coronary atherosclerotic disease and may be useful for noninvasively defining the role of established and new cardiovascular risk factors in selected patient groups.

Methods. A total of 211 consecutive patients, 26 to 79 years old, referred for evaluation of suspected or recently diagnosed coronary artery disease were examined. Selective coronary angiography was used to define five angiographic disease categories: normal coronary arteries, nonobstructive disease and one-, two- or three-vessel disease. EBCT was used to calculate coronary calcium scores, and cardiovascular risk, including lipid variables and fibrinogen levels, was assessed.

Results. Coronary calcium score and angiographic disease severity categories were largely predicted by identical risk factors (i.e., age, male gender, total/high density lipoprotein cholesterol ratio, fibrinogen) and, to a lesser degree, hypertension. Only smoking predicted angiographic disease severity but not calcium scores. The risk factors together explained a comparable proportion of the variability in angiographic disease categories and in calcium score quintiles (33% vs. 41%, p = 0.16 by bootstrap analysis). An overall risk score composed of these risk factors separated angiographic disease categories and calcium score quintiles with a similar area under the receiver operating characteristic curve ([mean ± SE] 0.81 ± 0.03 vs. 0.83 ± 0.03, p = NS).

Conclusions. Quantification of coronary calcium is comparable to selective coronary angiography in measuring the effect of established cardiovascular risk factors on coronary atherosclerosis. Thus, EBCT may be useful for the noninvasive evaluation of the relations between conventional or developing cardiovascular risk factors and coronary atherosclerosis.

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Coronary plaque formation is a complex consequence to genetic, environmental, dietary and habitual risk factor exposure. Acting through different mechanisms, coronary risk factors lead to endothelial injury, plaque formation and the promotion of arterial thrombus deposition (1). These risk factors are independent variables whose clinical impact is based on the development or progression of atherosclerosis (i.e., a specific pathophysiologic dependent variable) (2). With regard to a more accurate definition of coronary artery disease, the evaluation of risk factor associations with measurements of anatomic coronary atherosclerotic disease offers some advantages over clinical end points, such as myocardial infarction or sudden cardiac death (2,3). Selective coronary angiography is the standard clinical method for measuring the extent of anatomic coronary atherosclerotic disease. Alternative, noninvasive procedures would be attractive because of the potential for broader applications. However, currently available techniques (e.g., carotid two-dimensional ultrasound) do not directly visualize the coronary arteries (2) and thus may not always accurately reflect the coronary atherosclerotic disease process (4,5).

Electron beam computed tomography (EBCT) permits direct high resolution imaging of the coronary arteries in the beating heart. EBCT currently represents the only noninvasive method for accurate quantification of coronary artery calcium (6–8). Coronary artery calcium has been established as a specific expression of underlying atherosclerotic disease in

pathologic-anatomic studies (9,10). More recently, calcification has been suggested to represent an active, regulated process (11–13) that can be found in stages of atherogenesis seen in young adults (14,15). Quantification of coronary calcium by EBCT has been shown to provide a measure of mural atherosclerotic plaque burden (7,16,17), and a linear relation between coronary calcium area determined by EBCT and coronary plaque area has been reported (16). Thus, EBCT is of interest as a method for the noninvasive delineation of anatomic coronary atherosclerotic disease. However, the association of risk factors with coronary calcium compared with the standard measure of anatomic coronary atherosclerotic disease—coronary angiography—has not been examined. Consequently, the usefulness of EBCT for defining the role of established and new cardiovascular risk factors noninvasively remains unclear. The current study was therefore undertaken to determine whether the effect of established risk factors on anatomic coronary atherosclerotic disease was comparable as measured by 1) coronary angiography, and 2) quantification of coronary calcium by EBCT in patients with suspected or recently diagnosed coronary artery disease.

Methods

Patients. Two hundred eleven consecutive patients referred to the University Clinic Essen for coronary angiography as part of an evaluation for coronary artery disease were included in the study. The patients were examined between March 1994 and March 1996 and included only clinically stable patients scheduled to undergo elective coronary angiography during selected periods in which the EBCT scanner was available for this study. One hundred forty-six patients had suspected coronary artery disease and were referred for angiography because of angina-like chest pain (n = 22) or a positive exercise test (n = 53), or both (n = 71). The other 65 patients had previously undergone coronary angiography (n = 31) or a first myocardial infarction (n = 14), or both (n = 20), a maximum of 12 months and a minimum of 1 month before the current study. EBCT was performed within 1 week of angiography. Patients concurrently receiving lipid-lowering medications prescribed by their physicians were excluded from investigation because of the anticipated alteration of blood lipid variables. Additionally, patients with previous bypass surgery, coronary stent implantation, coronary rotablation or atherectomy were excluded because these interventions potentially affect quantification of coronary calcium by EBCT. Previous coronary angioplasty (n = 45) was not considered an exclusion criterion because it has been shown not to alter EBCT calcium measurements (18).

Risk factors. Risk factor assessment included evaluation of family history of premature myocardial infarction (occurring at an age ≤55 years in a parent or sibling), past or current smoking, diabetes mellitus, hypertension, calculation of body mass index and the laboratory measurements described below. *Hypertension* was established if standard sphygmomanometric measurements with patients at rest in the supine position showed systolic and diastolic blood pressure values ≥140 mm Hg and ≥90 mm Hg, respectively, on three occasions or if patients were receiving antihypertensive treatment, or both (19). *Diabetes* was defined as repeated blood glucose values ≥140 mg/dl or the use of antidiabetic drug treatment, or both. On admission, after ≥12 h of fasting, blood was drawn for direct laboratory measurements. Total cholesterol and triglycerides were measured using enzymatic assays and the oxidase technique (Technicon Dax System, Technicon). High density lipoprotein (HDL) cholesterol was determined by dextran sulfate-magnesium precipitation, followed by enzymatic measurement of cholesterol. Low density lipoprotein cholesterol was determined by precipitation with polyvinyl sulfate and ultracentrifugation (Boehringer Mannheim, Mannheim, Germany). Apolipoprotein (apo) A1, apoB and lipoprotein(a) were quantitated by nephelometry after addition of an antiserum (Behringwerke AG, Marburg, Germany) (20). Fibrinogen was measured by determining the coagulation time of prediluted citrated plasma in the presence of a large amount of thrombin (Behringwerke AG) and plasma glucose concentration using the glucose oxidase method. Precision (coefficients of variations) and accuracy (deviations from target values) of all measurements were in accordance with the legal guidelines for medical laboratories in Germany.

Coronary angiography. Selective coronary angiography was performed in each patient by the Judkins technique. After intracoronary injection of nitroglycerin (0.2 mg), a minimum of three biplane projections for the left coronary system and two biplane projections for the right coronary artery were obtained using a HICOR system (Siemens). *Significant stenosis* was defined as lumen narrowing ≥50% in any vessel. Off-line quantitative coronary angiography (MEDIS, Reiber) was used to confirm categorization of lesions and to characterize culprit lesions (21). The Coronary Artery Surgery Study (CASS) (22) definition of angiographic disease categories was used. Angiograms were classified into one of five categories: 1) angiographically normal coronary arteries, 2) lumen irregularities or nonobstructive stenoses representing <50% diameter reduction, 3) significant stenoses in one of the major coronary artery, 4) significant stenoses in two of the major coronary arteries, and 5) significant stenoses in three of the major coronary arteries or significant left main stem stenosis, or both.

EBCT. All patients gave informed consent to undergo the EBCT examination, which was performed with a Siemens Evolution scanner in the high resolution, single-slice mode with continuous, nonoverlapping slices of 3-mm thickness and an acquisition time of 100 ms. Patients were supine, and after

Table 1. Patient Characteristics: Risk Factor Variables in 211 Patients

Risk Factors (continuous variables)	Mean ± SD	Range	Median (25th, 75th percentile)	Cutpoints	No. (%) of Patients
Age (yr)	55.8 ± 10.4	26–79	56 (50, 63)	≥ 50 yr	152 (72%)
BMI (kg/m^2)	26.2 ± 3.1	18.8–36.1	25.9 (24.1, 27.9)	≥ 27 kg/m^2	76 (36%)
TC (mg/dl)	231.6 ± 48.9	101–418	230 (199, 265)	≥ 200 mg/dl	157 (74%)
HDL-C (mg/dl)	47.0 ± 13.0	20–103	46 (38, 55)	< 35 mg/dl	33 (16%)
TC/HDL-C ratio	5.3 ± 1.8	2.3–11.6	5.0 (3.9, 6.1)	≥ 5	108 (51%)
LDL-C (mg/dl)	170.7 ± 43.4	60–288	168 (138.5, 203.8)	≥ 130 mg/dl	169 (80%)
TGs (mg/dl)	172.9 ± 90.7	51–597	155 (113, 208.5)	≥ 200 mg/dl	61 (29%)
ApoA1 (mg/dl)*	146.7 ± 27.2	82.3–225.1	144.0 (127.5, 166.4)	< 140 mg/dl	77/181 (43%)
ApoB (mg/dl)*	129.7 ± 32.6	53.7–218.0	128.0 (104.0, 147.3)	≥ 120 mg/dl	108/181 (60%)
ApoA1/ApoB ratio*	1.2 ± 0.4	0.42–2.61	1.15 (0.92, 1.44)	—	—
Fibrinogen (mg/dl)	339.4 ± 84.7	188–719	328 (282, 384)	≥ 350 mg/dl	81 (38%)
Lp(a) (mg/dl)	45.9 ± 32†	<10.6–147	<10.6 (<10.6, 28.4)	≥ 30 mg/dl	51 (24%)
Male gender					169 (80%)
Family Hx (premature CAD)					55 (26%)
Smoking					126 (60%)
HTN					141 (67%)
DM					33 (16%)

*Measurements for only 181 (86%) of 211 patients. †Mean value for only 88 (42%) of 211 patients with lipoprotein(a) levels above the detection limit of 10.6 mg/dl; 123 patients (58%) had lipoprotein(a) levels <10.6 mg/dl. ApoA1 = apolipoprotein A1; ApoB = apoliprotein B; BMI = body mass index; CAD = coronary artery disease; DM = diabetes mellitus; HDL-C = high density lipoprotein cholesterol; HTN = hypertension; Hx = history; LDL-C = low density lipoprotein cholesterol; Lp(a) = lipoprotein(a); TC = total cholesterol; TGs = triglycerides.

localization of the main pulmonary artery, 36 to 40 slices caudad through the apex of the heart were obtained with electrocardiographic triggering at 80% of the RR interval. The presence of coronary calcium was sequentially evaluated in all levels, as previously described (17,23). The threshold for calcific lesions was set at a CT density of 130 Hounsfield units in an area of at least 0.52 mm^2 (2 pixels, 512^2 pixel matrix and 26 cm field of view) (5). A lesion score was determined by multiplying the area of the hyperattenuating lesion with a density factor as described by Agatston et al. (5). Calcium scores in each of the major epicardial coronary arteries were summed to define a total coronary artery calcium score.

Statistical analysis. Statistical analyses were performed using SPSS (version 6.1.4, SPSS Inc.) and SAS (version 6.08, SAS Institute) software packages and an IBM-compatible personal computer. Results are expressed as mean value ± SD, unless otherwise indicated. To account for the nonnormal distribution of total calcium scores, a log$_{10}${x + 1} transformation was made (24). Triglyceride values were also transformed to the logarithmic scale to minimize the skewness of distributions. Total HDL cholesterol and apoA1/apoB ratios were computed to account for the relative importance of these lipoprotein and apoprotein subfractions (25,26).

Multiple linear regression analysis was used to examine the independent relation of risk factors to angiographic disease categories and calcium scores. Coronary calcium scores were categorized into score quintiles to allow better comparisons with the five angiographic disease categories. The main risk factor predictors of angiographic disease categories and calcium score quintiles were determined by stepwise linear regression analysis, requiring alpha values of 0.05 and 0.10 for a

variable to enter and remain in the regression model. Risk factors not remaining in the model were added to the final model separately (in turn) to determine their partial significance. The R^2 value (the coefficient of determination) is a measure of how well the regression model describes the data. It was interpreted as explaining the proportion of variability in the dependent variables (angiographic disease categories or calcium score quintiles) accounted for by the (independent) risk factor variables (27). A bootstrap analysis (28) was performed to determine the significance of the difference in R^2 values between angiographic disease categories and calcium score quintiles. This method tries to replicate the variability in the original sample as a sample from a larger population. Each "bootstrap" sample is a random sample of 211 observations from the original set of 211 observations, where the same observation can be drawn more than once ("with replacement"). Five hundred bootstrap samples were drawn, and the R^2 values for both dependent variables were calculated and compared.

Receiver operating characteristic (ROC) curve analysis was performed to establish how well the overall risk found in the patients could separate angiographic disease categories on the one hand and calcium score quintiles on the other. To delineate overall risk for the ROC curve analysis, a simple risk score was constructed by inspection of the regression analysis, as explained in Results and the Appendix. Dichotomous angiographic disease categories (no or nonobstructive disease vs. one- to three-vessel disease) and calcium score quintiles (lower two quintiles vs. upper three quintiles) were used. Sensitivity as the dependent y-variable was plotted as a function of 1 − specificity as the x-variable (equivalent to the "false positive

Table 2. Patient Characteristics: Coronary Angiographic Findings and Coronary Calcium Scores for 211 Study Patients

Angiographic disease category	
Normal coronary arteries	59 (28%)
Nonobstructive disease	26 (12%)
One-vessel disease	61 (29%)
Two-vessel disease	31 (15%)
Three-vessel disease	34 (16%)
Calcium score	
Mean ± SD	274.2 ± 424.5
Median	77.9
25th percentile	1.6
75th percentile	347.4
Range	0–2,203.5
Quintile (range)	
1st	0–0.5
2nd	0.8–31.3
3rd	32.0–184.8
4th	186.7–437.4
5th	444.3–2,203.5

Data presented are number (%) of patients, unless otherwise indicated.

rate") to determine individual {x,y} pairs with different overall risk. A p value < 0.05 was considered significant for all statistical evaluations.

Results

Demographics. Patient characteristics and the distributions of angiographic disease categories and calcium scores are summarized in Tables 1 and 2. There was no difference in the mean age of men versus women (56 ± 10 vs. 57 ± 11 years, p = 0.48). Of the 211 patients, 126 (60%) had angiographically significant stenoses in at least one vessel; 172 patients (81%) had a total calcium score >0.

Figure 1. Independent risk factor predictors for patients with versus those without angiographically significant stenoses. TC = total cholesterol. *p < 0.05. †p < 0.001.
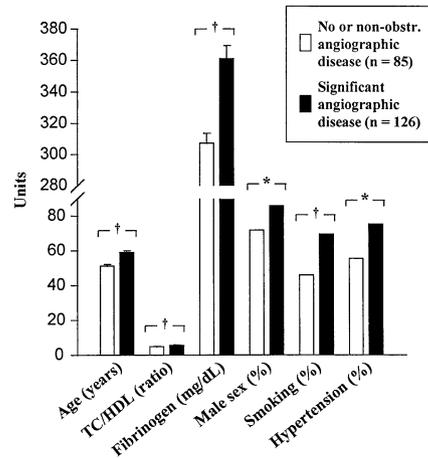
Risk factor associations. Independent risk factor associations with angiographic disease categories and calcium score quintiles are given in Tables 3 and 4. Age, gender, fibrinogen levels and the total/HDL cholesterol ratio were significantly associated with both measures of anatomic coronary atherosclerotic disease. Hypertension was of borderline significance in both models. However, smoking was associated only with angiographic disease severity. The R^2 values indicated that 33% of the variability in angiographic disease categories and 41% of the variability in calcium score quintiles were explained by risk factors. Bootstrap analysis indicated that the proportion of variability in calcium score quintiles explained by risk factors, although higher than for angiographic disease categories, was not statistically different (two-tailed p = 0.16). In

Table 3. Risk Factor Associations With Angiographic Disease Severity by Multiple Linear Regression Analysis*

Variable	Coeff	SE	T Value	p Value
Age (yr)	0.045	0.0084	5.34	< 0.001
TC/HDL-C ratio	0.098	0.048	2.05	0.042
Fibrinogen (mg/dl)	0.0028	0.0010	2.74	0.0066
Male gender	0.44	0.22	2.01	0.046
Smoking	0.56	0.18	3.20	0.0016
HTN	0.35	0.18	1.93	0.055
BMI (kg/m²)				0.38
TC (mg/dl)				0.30
HDL-C (mg/dl)				0.31
LDL-C (mg/dl)				0.094
TGs (mg/dl)				0.85
ApoA1†				0.20
ApoB†				0.23
Lp(a) (mg/dl)				0.090
Family Hx				0.43
DM				0.91

*Intercept = −2.26 (SE 0.64); T = −3.51; p < 0.001. †Measurements of apoA1 and apoB were available for only 181 patients. Coeff = coefficient; other abbreviations as in Table 1.

Table 4. Risk Factor Associations With Electron Beam Computed Tomographic Total Calcium Score Quintiles by Multiple Linear Regression Analysis*

Variable	Coeff	SE	T Value	p Value
Age (yr)	0.051	0.0078	6.52	< 0.001
TC/HDL-C ratio	0.18	0.044	4.00	< 0.001
Fibrinogen (mg/dl)	0.0038	0.00095	4.01	< 0.001
Male gender	0.61	0.20	3.10	0.0024
Smoking	—	—	—	0.54
HTN	0.34	0.17	2.02	0.045
BMI (kg/m²)				0.69
TC (mg/dl)				0.13
HDL-C (mg/dl)				0.23
LDL-C (mg/dl)				0.45
TGs (mg/dl)				0.97
ApoA1†				0.05
ApoB†				0.60
Lp(a) (mg/dl)				0.55
Family Hx				0.65
DM				0.99

*Intercept = −2.09 (SE 0.45); T = −4.68; p < 0.001. †Measurements of apoA1 and apoB were available only for 181 patients. Abbreviations as in Tables 1 and 3.
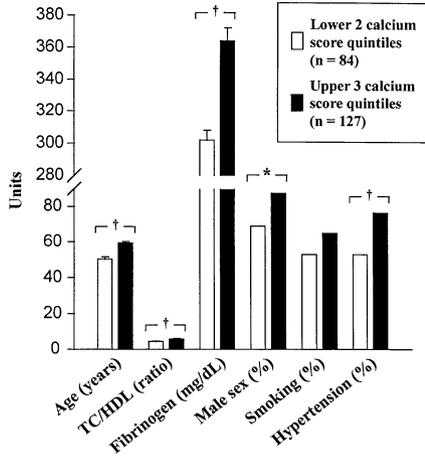
Figure 2. Independent risk factor predictors for patients with calcium scores in the upper three quintiles versus those with calcium scores in the lower two quintiles. TC = total cholesterol. *p < 0.05. †p < 0.001.

Figure 3. ROC curve analysis for overall risk score versus coronary angiographic findings (i.e., no or nonobstructive disease vs. significant angiographic disease) and calcium score quintiles (i.e., lower two quintiles vs. upper three quintiles). The sensitivity of the risk score with reference to coronary angiographic findings or calcium score is plotted as a function of {1 − specificity} (equivalent to the "false positive rate") to determine individual {x,y} pairs with different risk scores. The areas under the curve for coronary angiographic findings and calcium score are presented as mean ± SE and were not statistically different. Both curve areas were significantly different from a random distribution (coronary angiographic findings: p < 0.001, z = 10.59; calcium score: p < 0.001, z = 10.88).

Figure 1 the mean values or prevalence of the independent risk factor predictors are compared between patients with and patients without angiographically significant stenoses. In Figure 2 the same risk factor predictors are compared between patients with calcium scores in the upper three quintiles and patients with calcium scores in the lower two quintiles, with an almost identical number of patients per group as in the two angiographic groups in Figure 1.

When the regression models were compared, there was a distinct similarity in the coefficients predicting angiographic disease categories and calcium score (Tables 3 and 4). Because the range of both the coronary disease categories and the calcium score quintiles was one to five, the regression coefficients had a similar interpretation and could be used to construct a simple risk score representing the overall risk that determined the extent of anatomic coronary atherosclerotic disease in our patients (see Appendix). ROC curve analysis was performed to determine how well this overall risk score could separate angiographic disease, categorized into no or nonobstructive disease versus significant disease, and calcium scores, categorized into the two lower quintiles versus the three upper quintiles. Figure 3 shows that the area under the ROC curve for angiographic disease categories was comparable to that for calcium score quintiles (0.81 ± 0.03, vs. 0.83 ± 0.03, p = NS by bootstrap analysis). Figure 4 shows that the overall risk increased continuously with the five angiographic disease categories as well as with the calcium score quintiles.

Discussion

The present investigation demonstrates that clinical measures of established cardiovascular risk factors have a very similar relation with coronary calcium scores compared with angiographic disease categories in symptomatic patients. Smoking notwithstanding, five risk factors, (i.e., age, gender, fibrinogen, the total/HDL cholesterol ratio and, to a lesser degree, hypertension) were found to predict both measures of
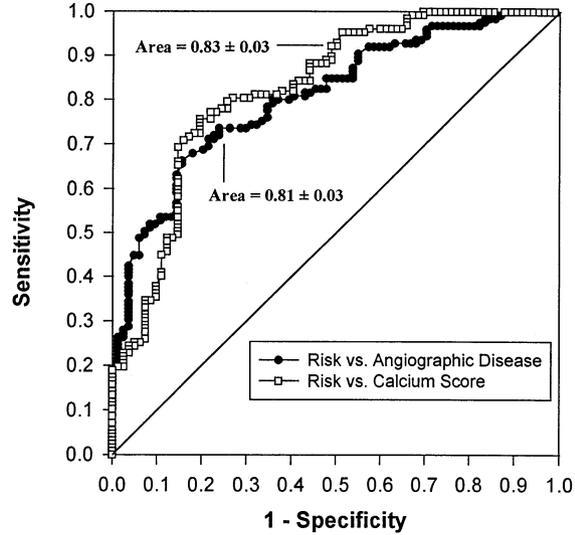
anatomic coronary atherosclerotic disease to a comparable degree. Hence, in the symptomatic cohort examined, quantification of coronary calcium by EBCT was comparable to coronary angiography in measuring the effect of established risk factors on anatomic coronary atherosclerotic disease. This finding may be of considerable importance for epidemiologic purposes because EBCT may thus be the first noninvasive

Figure 4. Overall risk score (±SD) in the five angiographic disease categories (**solid bars**) versus calcium score quintiles (**open bars**). Overall risk increases continuously and similarly in each category for both angiographic disease categories and coronary calcium score quintiles. *p < 0.05 (analysis of variance, Student-Newman-Keuls test).
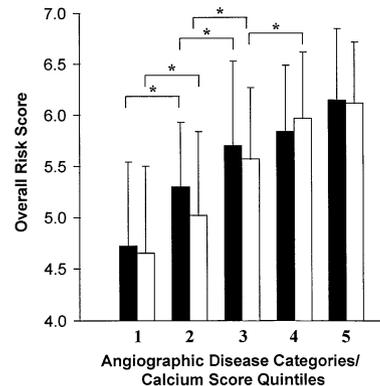
method that allows direct evaluation of the effects of risk factors on coronary atherosclerosis.

Coronary calcium and atherosclerosis. Several mechanisms link arterial calcification to atherosclerosis (11–13). Cholesterol and its oxidation products accelerate coronary calcification (12). Smaller amounts of calcium have been shown to be present in noncomplex, lipid-rich fibromuscular plaques (10) and in coronary lesions seen in young adults (type III lesion) (14). More advanced type Vb/VII plaques regularly contain calcium deposits (14,15). Although calcium quantities are best correlated with overall coronary plaque area (16,29), a positive correlation with stenosis severity is also seen (30), establishing the potential for noninvasive diagnosis of coronary stenoses (31). In contrast, even severe stenoses are occasionally noncalcified as assessed by EBCT (7,17,23). Coronary angiography very reliably detects flow-limiting stenoses. Overall plaque burden may be underestimated because of mechanisms such as arterial remodeling, a diffuse distribution of atherosclerotic disease and eccentric lesion formation (1,32,33). In this respect, sophisticated angiographic scoring methods seem to offer only limited incremental value (32,34,35).

Risk factor variables. Smoking was independently associated with angiographic disease but not with coronary calcium score. Smoking is a risk factor for coronary arterial thrombosis irrespective of plaque morphology (36), and it may lead to clinical symptoms at earlier stages of coronary artery disease than in nonsmokers (37). Accordingly, smokers with a comparably low coronary plaque burden and little or no calcification may become symptomatic.

An interesting finding in our study group was the strong independent predictive value of fibrinogen levels with respect to both calcium scores and angiographic disease categories. It has been previously shown that elevated fibrinogen levels independently predict cardiovascular events (38) and angiographic disease severity (39). Its role as an indicator of inflammation notwithstanding, elevated fibrinogen levels can be considered a major cardiovascular risk factor (40).

Study limitations. Despite substantial advances in our knowledge in recent years, the multifactorial pathogenic mechanisms of atherogenesis are still incompletely understood. Numerous coronary risk factors have been proposed. Homocysteine (41) was not measured in the present investigation. It has adverse effects on endothelium, platelets and clotting factors, and elevated homocysteine concentrations have been associated with premature coronary artery disease and myocardial infarction. Another genetic risk factor, apoE polymorphism (42), was also not considered. Furthermore, recent reports (43) have suggested that chronic infection with agents such as *Chlamydia pneumoniae* may play a role in vascular endothelial damage and atherogenesis. These and other risk factors may account for part of the unexplained variability in measures of coronary atherosclerosis (44). Nonetheless, to our knowledge, our investigation represents the most comprehensive risk assessment with regard to coronary calcium quantities thus far reported.

The study group was relatively small (n = 211), and a larger study group might have enabled the detection of differences in the correlations of risk factors with coronary calcium scores versus angiographic disease categories. However, given that there was a trend in favor of coronary calcium that might have become more obvious in a larger sample, our main conclusions regarding the value of coronary calcium as a measure of risk factor effects on coronary atherosclerosis would only be strengthened.

It should be noted that the present study examined a cohort sample from an urban area in Germany. Extrapolation to other patient groups may be limited, especially with regard to smoking habits.

Clinical implications. Our results suggest that noninvasive quantification of coronary artery calcium by EBCT may allow for facilitated, noninvasive measurements of anatomic coronary atherosclerotic disease in epidemiologic investigations. The close link between coronary risk factors and coronary calcium as a measure of atherosclerotic disease is also underscored by recent EBCT studies in symptomatic (24) and asymptomatic (45,46) high risk patients that reported that high calcium scores predicted death and myocardial infarction (24) and other cardiovascular events (45,46) in these study groups. Thus, EBCT may allow noninvasive evaluation of the relation between conventional or developing cardiovascular risk factors and coronary atherosclerosis.

Appendix

Overall Risk Score

The overall risk score was based on the cardiovascular risk factors that were found to predict angiographic disease categories and calcium scores in our patient sample and were calculated as follows:

$$\text{Overall risk} = \frac{\text{Age}}{20} + \frac{(TC)/(HDL)}{10} + 1\{\text{Male}\}\cdot 0.5 + \frac{\text{Fbg}}{350} + 1\{\text{Smoker}\}\cdot 0.5$$
$$+ 1\{\text{HTN}\}\cdot 0.7,$$

where Fbg = fibrinogen (mg/dl); HDL = HDL cholesterol; HTN = hypertension; and TC = total cholesterol. For a 20-year old nonsmoking, nonhypertensive woman with a ratio of total cholesterol/HDL cholesterol of 3 and a fibrinogen level of 250 mg/dl, the risk score is 2.01. For a 70-year old hypertensive man with a ratio of total cholesterol/HDL-cholesterol of 7 and a fibrinogen level of 450 mg/dl and who smokes, the risk score is 6.84.

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