Use of electron beam tomography data to develop models for prediction of hard coronary events

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Background Prediction of hard cardiac events (myocardial infarction and coronary death) remains difficult in spite of the identification of several relevant risk factors for the development of coronary artery disease (CAD). New indicators of risk might add to our predictive ability. We used measures of coronary artery calcification (CAC) found by electron beam tomography (EBT) imaging to develop prediction models for hard cardiac events alone and in association with traditional risk factors for CAD.

Methods Two groups of patients were studied: group A, 676 asymptomatic patients (mean age 52 years, 51% men) prospectively followed up for 32 ± 7 months after being referred by primary care physicians for a screening EBT, and group B, 10,122 asymptomatic patients screened by EBT at one center and used as controls for calculation of calcium score nomograms.

Results The occurrence of hard events in group A patients was related to traditional risk factors for CAD, presence of CAC (score >0), Ln (1 + absolute calcium score [CS]), and age- and sex-specific CS percentiles (CS%). Univariate analyses showed that age, smoking, diabetes mellitus, presence of CAC, Ln (1 + absolute CS), and CS% were predictive of hard events (all $P < .05$). Multiple logistic regression analyses demonstrated that CS% was the only significant predictor of events and provided incremental prognostic value when added to traditional risk factors for CAD (chi-square, $P < .001$). In a comparison of receiver-operator characteristic curves for prediction of hard events, the area under the curve for CS% plus conventional risk factors and age was significantly larger than that obtained by use of traditional risk factors and age separately as predictors (0.84 vs 0.71, respectively, $P < .001$). Furthermore, the area under the curve of CS% alone was significantly larger than that of traditional risk factors and age combined (0.82 vs 0.71, $P = .028$).

Conclusions Patients are usually selected for EBT screening on the basis of the presence of conventional risk factors for CAD. However, an age- and sex-specific calcium score provides the best predictive model for the occurrence of hard coronary events and adds incremental prognostic information to conventional risk factors for CAD. (Am Heart J 2001;141:375-82.)

Prediction of hard coronary artery disease (CAD) events remains difficult in spite of the identification of several risk factors for the development of atherosclerotic heart disease and markers of plaque instability.[1,2] In a pursuit for solutions to this difficult task, investigators have recently focused on several noninvasive imaging modalities with the ability to identify atherosclerotic disease in its preclinical stages.[3-6] The question remains whether discovery of atherosclerotic disease in an early phase of development may provide relevant prognostic information for the prediction of hard cardiovascular end points (myocardial infarction or cardiac death). Electron beam tomography (EBT) allows the visualization of coronary artery calcification (CAC), a known marker of underlying atherosclerosis. The extent of calcium deposits is estimated by means of a calcium score that bears a close correlation to the atherosclerotic plaque burden.[7-10] Previous investigations have dealt with the prognostic impact of CAC discovered on a screening EBT study with controversial results. Arad et al[11] showed that the odds ratios for a variety of cardiovascular events, including revascularization procedures, stroke, myocardial infarction, and death, range between 20 and 35 in the presence of various degrees of calcification on a screening test. In a recent publication we reported that the majority of asymptomatic patients screened by EBT who have a hard coronary event have high age- and sex-specific calcium score percentiles on their initial scans.[12] Other investigators have questioned the predictive value of CAC, especially for subsequent

Table I. Clinical characteristics and annual absolute risk of a fatal or nonfatal myocardial infarction for patient groups in the prospective cohort

	Patients without events (n = 646)	Patients with events (n = 30)	Annual absolute risk when categorical factor is present (%)
Men	328 (51%)	16 (53%)	1.7
Mean age (y)	52 ± 16*	55 ± 8*	–
Smoking	255 (40%)†	20 (67%)†	2.7
Diabetes mellitus	66 (10%)‡	7 (23%)‡	3.6
Systemic hypertension	303 (47%)‡	18 (60%)‡	2.1
Hypercholesterolemia	371 (57%)‡	21 (60%)‡	2.0
CAC on EBT (CS >0)	328 (51%)§	29 (97%)§	3.0
No CAC on EBT	318 (49%)	1 (3%)	0.12
Mean CS (±SD)	87 ± 234‖	388 ± 696‖	

CS, Calcium score.
*P < .05.
†P <.01.
‡Not significant.
§P < .001.
‖P = .025.

myocardial infarction and coronary death.[13-16] The American Heart Association Prevention Conference V[17] recommended against the routine use of EBT screening in asymptomatic patients but encouraged further research in this field. The document also suggested that the greatest potential for coronary calcium screening lies in the detection of atherosclerosis in asymptomatic individuals at intermediate risk. Similar conclusions were reached by a consensus panel of the American College of Cardiology and American Heart Association.[18]

In the current analysis we intended to verify whether measures of coronary calcification could be used to develop models for prediction of hard cardiac events. In so doing, we were also interested to know whether data collected by means of EBT imaging add incremental prognostic information to that provided by risk factors for CAD. Six hundred seventy-six asymptomatic patients referred by primary care physicians for EBT screening were followed up for a mean of 32 ± 7 months. Data on these patients were used in part for a previous publication.[12] The occurrence of hard coronary events was correlated with the presence of categorical risk factors for CAD at baseline and both absolute calcium scores and age- and sex-specific calcium score percentiles.

Methods
Patient selection
A screening EBT was performed in 676 patients referred by primary care physicians because of the presence of risk fac-

tors for CAD (Table I). Clinical follow-up for cardiac events was done by telephone interview at a mean of 32 ± 7 months (range 24 to 48 months) from the initial screening, and all reported events were verified by means of medical record and death certificate review where appropriate. Diagnosis of myocardial infarction was confirmed by means of standard clinical, electrocardiographic, and plasma MB creatine kinase criteria.[19,20] Both Q- and non-Q-wave myocardial infarctions were included in this study. Patient mean age at the time of screening was 52 ± 10 years. All patients signed an informed consent before undergoing EBT imaging. Data on risk factors for CAD were collected by a cardiac nurse before the initial EBT imaging procedure. Arterial hypertension was defined by current use of antihypertensive medications or known but untreated hypertension. Current smoking was necessary for the definition of positive smoking status. Hypercholesterolemia was defined as currently receiving cholesterol-lowering medications or the presence of known but untreated hypercholesterolemia. Patients currently receiving insulin or oral hypoglycemic agents were classified as diabetic. Our use of risk factor categories instead of continuous variables may seem inadequate. However, in a recent reanalysis of the Framingham data Wilson et al[21] showed that the use of such categories as normal or high blood pressure, normal or high cholesterol, smoking versus nonsmoking, and diabetes versus nondiabetes is an acceptable way to asses an individual's risk of cardiovascular events. Furthermore, self-reporting of risk factors by individual patients has been shown to be reliable and accurate.[22] Therefore we believe that our use of risk categories for the purpose of conducting the current study was appropriate.

Imaging protocol
Patients underwent EBT imaging with an Imatron C-100 scanner (Imatron, South San Francisco, Calif). Images were obtained with 100-ms scan time and 3-mm single slice thickness, with a total of 40 slices starting at the level of the carina and proceeding to the level of the diaphragm. Tomographic imaging was electrocardiographically triggered at 80% of the RR interval. An imaging field of view of 30 cm² was used (pixel size 0.586 mm) and the definition of coronary calcification required the presence of at least 3 contiguous pixels (area 1.03 mm²) with density ≥130 HU. Quantitative calcium scores (CS) were calculated according to the method described by Agatston et al.[7] This study was begun before we introduced a new and more reproducible volumetric calcium score[23]; therefore we could not use this novel measurement tool. Furthermore, all other studies on outcome of patients submitted to EBT imaging have so far used the traditional CS and our intention was to conduct an analysis with comparable tools.

Statistical analysis
The calcium scores of 10,122 asymptomatic individuals who underwent EBT screening according to the same imaging protocol as the study patients were used for the creation of tables of CS percentiles (Table II). We calculated percentiles using only CSs >0. This was done to potentially reduce the effect of referral bias. In fact, referring large numbers of patients with a low pretest likelihood of disease may skew the percentiles toward lower values if all 0 scores were included.

Table II. CS percentiles for 5089 patients with positive scores, among 10,122 consecutive asymptomatic patients

Age (y)	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-70
Women (n = 4438)								
No.	134	288	589	822	903	693	515	485
% with CS >0	10	15	21	25	37	48	56	70
Percentile								
10	2	3	3	3	3	5	4	5
20	3	3	3	4	6	8	10	12
30	3	3	4	7	10	12	20	27
40	4	5	6	10	14	25	37	45
50	4	7	8	15	24	36	59	79
60	9	15	12	23	41	55	101	103
70	9	26	23	40	60	86	174	169
80	14	48	33	78	89	158	269	255
90	46	55	70	119	177	275	499	462
Men (n = 5684)								
No.	251	479	859	1066	1085	853	613	478
% with CS >0	18	27	40	56	66	77	83	88
Percentile								
10	3	2	4	3	7	6	17	16
20	3	3	6	6	12	15	37	41
30	4	5	8	10	24	29	67	85
40	5	8	12	19	38	51	121	134
50	6	12	20	34	59	79	194	221
60	7	18	32	52	93	127	301	326
70	9	26	42	83	138	211	439	520
80	13	47	82	149	232	340	556	784
90	56	116	176	323	449	660	925	1218

The reverse would be true if the referral was biased in favor of patients with a high pretest likelihood of disease. Therefore, by excluding the 0 values, we attempted to produce tables more indicative of the true epidemiology of CAC in the population. Table II therefore differs from a table we previously published where the 0 scores where included.[12] We then proceeded to assign an age- and sex-specific CS percentile (CS%) to each member of the prospective patient group. For each patient, the CS% was defined as the proportion of asymptomatic patients with CAC, who were of the same sex and age (±2 years) and who had a CS below that of the subject under study. Table II provides a summary of the CS deciles among patients with CAC in the asymptomatic reference sample. Risk factors for coronary artery disease in this large cohort were represented as follows: diabetes mellitus 11%, systemic hypertension 47%, hypercholesterolemia 56%, and smoking 43%. Single and multiple predictor logistic analyses (binary outcome) were performed to determine how the relative risk of a hard event was marginally and jointly related to age, sex, CS, CS%, and indicators for 4 established risk factors for CAD (smoking, hypertension, diabetes mellitus, hypercholesterolemia). In addition, forward and backward stepwise logistic regression procedures[24] were used in the prospective patient sample to select predictors from among all traditional risk factors (in addition to sex and age), all 2-way risk-factor interactions (including all 2-way interactions with CS% and with presence of CAC), and predictor variables based on the number of risk factors present in addition to smoking. The Bayesian information criterion was used to evaluate the relative scientific value of each model.[25,26] Goodness-of-fit measures were used to evaluate the fit of all logistic models,

including area under the receiver-operater characteristic curve (ROC area), and in the case of models that included continuous variables, the Hosmer-Lemeshow chi-square test was used. Risk was assessed by odds ratios for fatal and nonfatal myocardial infarctions and absolute risk of events.

We estimated the ROC areas of the binary logistic models based on (1) age only, (2) age and other traditional risk factors, (3) age, other traditional risk factors, and CS%, (4) CS% alone. We then tested models (1), (2), and (3) for incremental value with use of the likelihood ratio statistic. Finally, the ROC curves of models (2) and (4) were graphed as a comparison of nonoverlapping diagnostic strategies and the difference in ROC areas was tested for significance with a nonparametric test for correlated ROC curves.[27]

Values are presented as mean ± SD. Statistical significance was defined as a *P* value <.05. For predictors, this was based on the 2-tailed test for whether the coefficient is significantly nonzero; all tests on proportions are also 2 tailed.

Results

Patient clinical characteristics are shown in Table I. Patients had an average of 1.6 risk factors for CAD (median 2). Thirty patients had 21 nonfatal myocardial infarctions and 9 coronary deaths. Table I shows the annual absolute risk of an event when a categorical risk was present. Patients with any amount of calcium (CS >0) showed an absolute risk of events of 3% per year, whereas the absolute risk for patients without CAC was 0.12%. In line with the fact that diabetes mellitus car-

Table III. Absolute event rates in relation to current smoking status and presence of CAC on a screening EBT

Smoking	CAC on screening EBT	Event rate (%)
No	No	0
Yes	No	0.97
No	Yes	5.4
Yes	Yes	11

ries a very high risk of events, comparable to that of patients who have had a prior myocardial infarction,[28] our diabetic patients also demonstrated a very high absolute risk of 3.6% per year.

The prevalence of CAC was higher in smokers (63% vs 46%, $P < .001$), patients with diabetes mellitus (75% vs 50%, $P < .001$), and patients with systemic hypertension (62% vs 45%, $P < .001$). Patients with events were older, had a higher prevalence of CAC (97% vs 51%, $P < .001$), had larger CS values (388 ± 696 vs 87 ± 234, $P = .025$), and were more often smokers (67% vs 40%, $P < .01$) than patients who did not have an event. The odds ratio for having a hard event in patients with CAC was 28-fold that of patients without CAC. Table III shows the influence of CAC and smoking, alone or in combination, in determining the occurrence of a hard event. The presence of CAC alone was associated with a higher event rate than smoking alone. However smoking added prognostic value to CAC: among patients with CAC, those who smoked had an event at a rate of 11% versus 5.4% for those who did not smoke (borderline significance with $P = .053$). All traditional risk factors and coronary calcification parameters were assessed by univariate analysis to determine their ability to predict subsequent coronary events. Of the predictors based on CS, the absolute CS was not included because it showed a very poor fit compared with $\ln(1 + \text{absolute CS})$ and CS%.

The single-predictor logistic regression analyses showed that age, smoking, diabetes mellitus, presence of CAC (CS >0), $\ln(1 + \text{absolute CS})$, and CS% were significant predictors of acute myocardial infarction and coronary death (Table IV). Note that although the odds ratios for categorical variables, such as smoking and diabetes mellitus, are directly applicable to the concept of risk estimation, the corresponding ratios for age and the two predictors based on continuous CS values reflect the change in odds per unit change in these predictors. Among univariate models based on CS, CS% yielded the largest log-likelihood value and most favorable goodness-of-fit statistics. Also, $\ln(1 + \text{absolute CS})$ did not have incremental value beyond CS% ($P = .47$). Therefore CS% was the only variable based on CS that was chosen for inclusion in the multiple predictor analyses. CS% and all conventional risk factors in Table

IV were then used in forward and backward stepwise analyses. The only risk factor that approached significance when used with CS% was smoking ($P = .103$). In this 2-predictor model (right side of Table IV), CS% was still a significant predictor (odds ratio 1.03 per unit of CS%, 95% confidence interval [CI] 1.02-1.05; $P < .001$). We also tested the significance of the interaction of smoking with CAC (CS >0) and CS%. Neither interaction was significant when added to the above model ($P > .15$). Stepwise analyses demonstrated that the best scientific model was the univariate logistic regression on CS% considered alone (odds ratio 1.03, 95% CI 1.02-1.05). Among all risk variables and 2-way interactions considered, the only one that achieved significance ($P < .05$) when used in conjunction with CS% was the interaction of smoking and hypertension. In this 2-predictor model, the odds ratio associated with each unit increase in CS% was again 1.03 (95% CI 1.02-1.05), whereas the odds ratio for the smoking-hypertension interaction was 2.3 (95% CI 1.1-5.1).

For patients in each age- and sex-specific decile of CS, Table V shows the absolute risk and odds ratios of having a myocardial infarction on the basis of the logistic regression on CS% in the prospective sample.

By use of a likelihood ratio test, we determined that the predictor CS% provided significant incremental prognostic information when added to the traditional risk factors listed in Table IV ($P < .001$). Furthermore, because age is considered a substantial risk factor for cardiovascular events in the Framingham model, we tested whether CS% added incremental information over age or risk factors. Table VI summarizes the incremental value tests and corresponding ROC curve areas for models on the basis of age alone, age and other traditional risk factors, and age plus other conventional risk factors plus CS%, respectively (areas under the curve 0.61, 0.71, and 0.84, respectively). In each case the incremental values were significant and the maximum area under the curve was obtained when CS% was added to all other factors (Figure 1). Finally, Figure 2 provides a comparison of ROC curve on the basis of CS% only (total area 0.82, SE 0.048) with that of the model based on conventional risk factors plus age (total area 0.71, SE 0.054). The ROC curve area for CS% was significantly larger than that of traditional risk factors alone ($P = .028$, 2 tailed) indicating that in our patient cohort CS% was a better predictor of hard events than the presence of risk factors for atherosclerotic disease.

Discussion

In this prospective study of a cohort of asymptomatic patients, we sought to define the best model to identify patients at risk for development of hard coronary events. Univariate analyses showed that age, smoking, diabetes mellitus, and both absolute and relative measures of CAC were predictive. However, multiple logis-

Table IV. Risk of acute myocardial infarction (fatal and nonfatal) on the basis of logistic regression models in the prospective sample

Variable	Univariate logistic analyses			Multiple predictor logistic regression		
	Coefficient	P	Odds ratio (95% CI)	Coefficient	P	Odds ratio (95% CI)
Intercept	–	–	–	–4.89	.000	
Smoking	1.12	.005	3.1 (1.4-6.7)	0.67	.103	2.0 (0.9-4.4)
Diabetes	0.98	.029	2.7 (1.1-6.5)	–	–	–
Hypertension	0.53	NS	1.7 (0.8-3.6)	–	–	–
Hypercholesterolemia	0.54	NS	1.7 (0.8-3.8)	–	–	–
Male sex	0.10	NS	1.1 (0.5-2.3)	–	–	–
Age	0.039	.05	1.04 (1.0-1.1)	–	–	–
CAC	3.34	.001	28.1 (3.8-207.6)	–	–	–
ln(1 + CS)	0.49	.000	1.6 (1.4-2.0)	–	–	–
CS%	0.034	.000	1.03 (1.02-1.05)	0.032	.000	1.03 (1.02-1.05)

CI, Confidence interval; *NS,* Not significant.

Table V. Annual absolute risk for fatal and nonfatal myocardial infarction and odds ratio associated with each decile of CS according to the logistic model

CS%	Annual absolute risk (%)	Odds ratio (95% CI)
0	0.36	1.0 (1.0-1.0)
10	0.51	1.4 (1.2-1.6)
20	0.71	2.0 (1.6-2.5)
30	0.99	2.8 (1.9- 4.0)
40	1.38	3.9 (2.4-6.4)
50	1.92	5.5 (3.0-10.1)
60	2.64	7.8 (3.8-16.0)
70	3.62	10.9 (4.7-25.4)
80	4.90	15.4 (5.8-40.4)
90	6.54	21.6 (7.3-64.1)

Table VI. Summary of ROC curve areas and tests for incremental value

Predictors	ROC area	Incremental P value
Age	0.61	.050
Age plus traditional risk factors	0.71	<.001
Age plus traditional risk factors plus CS%	0.84	<.001

Figure 1

Comparison of three ROC curves based on (1) age alone *(very thick curve),* (2) age and other traditional risk factors (sex, smoking, diabetes mellitus, hypertension, and hypercholesterolemia, *thick curve),* and (3) age, other traditional risk factors, and CS% *(thin curve).*

tic regression analyses showed that the model based on CS% alone represented the best scientific model for prediction of events. Furthermore, CS% provided significant incremental prognostic information either alone or in combination with traditional risk factors for CAD for prediction of hard coronary events.

It is well known that the risk of cardiovascular events is proportional to the overall plaque burden and that the risk increases with advancing age.[29] Atherosclerotic plaque accumulates steadily as age increases and it is accompanied by a parallel expansion of the volume of coronary artery calcification.[10] EBT gives an objective assessment of the atherosclerotic plaque burden and the notion of CS percentile helps conceptualize the extent of disease found in a person relative to that of asymptomatic subjects of the same age and sex. Therefore it is a good representation of the developmental stage of coronary atherosclerosis in an individual patient and it seems reasonable that it would be a good predictor of hard events. The results of our study suggest that, although risk factors pose a risk for development of atherosclerotic heart disease, the presence of coronary calcification firmly establishes its presence in the arterial wall, with an attendant increased risk of a cardiovascular event. The American Heart Association Prevention V Conference and a recent American College of Cardiology/American Heart Association position

Figure 2
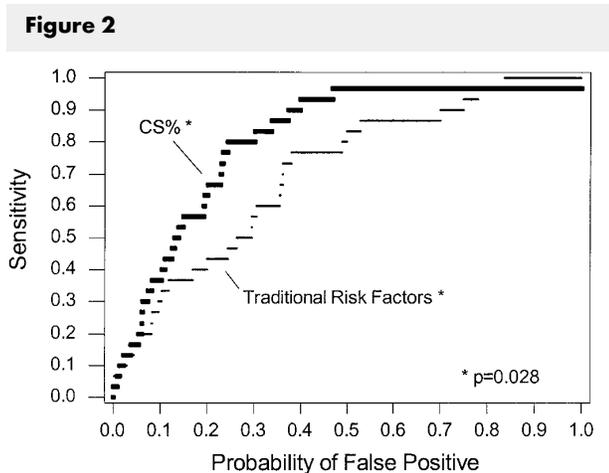
Comparison of the ROC curve on the basis of CS% alone with the ROC curve based on age plus 5 conventional risk factors (sex, smoking, diabetes mellitus, hypertension, hypercholesterolemia).

paper on EBT imaging expressed a negative opinion about the routine use of EBT imaging in clinical practice. However, they also suggested that this technology could find its best application in the study of asymptomatic patients at intermediate risk and encouraged further research in the field.[17-18] According to the guidelines of the European Society of Cardiology on prevention,[30] an absolute 10-year risk for cardiovascular disease ranging between 10% and 20% should be considered an intermediate risk level and above 20% the risk should be considered high. The absolute risk levels shown in Table I demonstrate that the patient cohort in our study carried at least a moderate to high risk for events, therefore corresponding to the appropriate population to be submitted to EBT imaging.[17,18] The main criticisms raised against the routine application of EBT imaging in the recent American College of Cardiology/American Heart Association statement were that (1) there is insufficient evidence that by identifying coronary calcification in asymptomatic individuals a physician may be able to conduct a better risk stratification than by using risk factors alone and (2) the sensitivity and specificity of this technology for the identification of obstructive coronary disease in symptomatic patients is suboptimal. Our study was not intended to address the latter criticism, but it provides at least a partial answer to the first criticism by showing that when appropriately applied coronary calcification imaging can actually improve risk prediction. The supporting paradigm of primary prevention is that evidence of significant plaque burden justifies aggressive medical intervention even in the absence of symptoms.[31] There-

fore the atherosclerotic plaque burden assumes the weight of a risk factor and, in fact, in our study calcium burden added significantly to the prognostic value of traditional risk factors. It is also obvious that the absence of calcium on coronary screening, even in the presence of risk factors, identifies a group of patients at very low risk of events and both the American College of Cardiology/American Heart Association writing group and the Prevention V Conference agreed that the negative predictive value of EBT is very high.[17,18] The importance of finding new predictors of risk is highlighted by the known suboptimal predictive value of conventional risk factors. Despite the use of a multifactorial approach to risk stratification, as advocated in the Framingham study and the National Cholesterol Education Program guidelines, more than 50% of the hard coronary events remain unpredictable and occur in patients at intermediate risk.[32] In the pursuit of better markers of disease, the value of coronary calcium screening as a risk stratification tool has been the focus of much debate. The original and most recent publication by Arad et al[11,33] supports the use of coronary calcium as a valid screening tool for prediction of cardiovascular events—both hard and soft events—in a population of asymptomatic and partially self-referred individuals. In both publications an absolute calcium score >160 was associated with high sensitivity and specificity and very high odds ratios for events. In a meta-analysis, O'Malley et al[34] noted that a calcium score above the median on a screening EBT study portends a risk ratio for hard coronary events 4.2 times that of patients without CAC and a risk ratio of 8.7 for combined soft and hard events. Similarly, in a recent publication by Wong et al[35] patients with an absolute CS in the upper 3rd and 4th quartiles showed a relative risk for cardiovascular events of 4.5 and 8.8 times that of patients in the lowest quartile, respectively. With use of Cox proportional-hazards they showed that patients with CAC had a greater risk of events than patients without CAC independent of age, sex, and risk factors. Raggi et al[12] demonstrated that patients in the upper quartile of CS% have a very high relative risk of events (51 times that of the 1st quartile) independent of the absolute CS values. In that analysis the authors provided an explanation for the apparent paradox of the occurrence of hard events in patients with low as well as high absolute CSs, as noted by Doherty et al.[36] The above referenced studies support the prognostic strength of calcium as a marker of preclinical disease and risk of cardiac events. Nonetheless, a publication by Detrano et al[16] seemed to refute this evidence. The authors studied a cohort composed mainly (89%) of male patients, who were older (mean age 66 ± 8 years) than patients used for any other published study and all patients were considered to be at high risk for coronary artery disease. Furthermore, the investigators used an

EBT imaging algorithm with a slice thickness of 6 mm; this protocol may have caused a substantial loss of information. In fact, its sensitivity is significantly inferior to that of the traditional 3-mm protocol for detection of CAC.[37] They concluded that the prognostic value of CAC as a predictor of hard coronary events was not better than that of traditional risk factors for CAD. However, although the majority of patients in the age range selected by Detrano et al are expected to show CAC on EBT imaging, in their study only 67% of the patients did, confirming the suspected reduced sensitivity of the imaging protocol used.[37] Therefore the missed imaging information likely weakened the prognostic power of CAC in the presence of a high prevalence of traditional risk factors for CAD.[37] In addition, the specificity of EBT for the prediction of hard coronary events is low in men after age 55 to 60 years.[38,39] Hence it was probably inappropriate to screen by EBT a population of older, high-risk men in an attempt to identify individuals at risk.

Grundy[29] recently suggested that, although the age factor is an essential indicator of risk, an objective estimation of the atherosclerotic plaque burden would strengthen its prognostic import. Therefore he further proposed to modify the Framingham formula, used to estimate an individual's absolute risk for CAD, by introducing a weight factor represented by the patient's CS percentile.[40] Hence an approach based on a combination of imaging data and risk factors, to include serologic markers of inflammation such as C-reactive protein, would offer an opportunity to direct more aggressive preventive measures to the patients at highest risk, with potentially improved outcome of primary prevention programs.

Whenever a new risk is proposed, it is essential to demonstrate that it adds to the predictive ability of previously established risk factors. This cannot be adequately achieved with univariate analyses alone but needs confirmation by means of more comprehensive multiple logistic regression models. In our study we used both approaches and confirmed by both means that CAC carries relevant prognostic information for the development of hard coronary events. The power of the predictor based on CS% was demonstrated by the consistency of its coefficient when other risk factors were added to the model and its appearance as the best event predictor across all models was tested. Nevertheless, these results are based on only 30 observed events and are therefore somewhat preliminary although several other reports have indicated similar trends.

We conclude that relative measures of CAC found on screening EBT studies offer incremental prognostic information that may improve our ability to predict CAD events. Conventional risk factors should be used to select patients for EBT screening, but age- and sex-specific CS%s should be used to enhance the physician's ability to estimate an individual patient's risk.

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