

Long-Term Prognostic Value of Coronary Calcification Detected by Electron-Beam Computed Tomography in Patients Undergoing Coronary Angiography

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Background—Electron-beam CT (EBCT) quantification of coronary artery calcification (CAC) allows noninvasive assessment of coronary atherosclerosis. We undertook a follow-up study to determine whether CAC extent, measured at the time of angiography by EBCT, predicted future hard cardiac events, comprising cardiac death and nonfatal myocardial infarction (MI). We also assessed the potential of selected coronary artery disease (CAD) risk factors, prior CAD event history (MI or revascularization), and angiographic findings (number of diseased vessels and overall disease burden) to predict subsequent hard events.

Methods and Results—Two hundred eighty-eight patients who underwent contemporaneous coronary angiography and EBCT scanning were contacted after a mean of 6.9 years. Vital status and history of MI during follow-up were determined. Cox proportional hazards models were used to compare the predictive ability of CAC extent with selected CAD risk factors, CAD event history, and angiographic findings. Median CAC score was 160 (range 0 to 7633). The 22 patients who experienced hard events during follow-up were older and had more extensive CAC and angiographic disease ($P<0.05$). Only 1 of 87 patients with CAC score <20 experienced a subsequent hard event during follow-up. Event-free survival was significantly higher for patients with CAC scores <100 than for those with scores ≥ 100 (relative risk 3.20; 95% CI 1.17 to 8.71). When a stepwise multivariable model was used, only age and CAC extent predicted hard events (risk ratios 1.72 and 1.88, respectively; $P<0.05$).

Conclusions—In patients undergoing angiography, CAC extent on EBCT is highly predictive of future hard cardiac events and adds valuable prognostic information. (*Circulation*. 2001;104:412-417.)

Key Words: angiography ■ calcium ■ coronary disease ■ imaging ■ prognosis

Calcific deposits in coronary arteries are pathognomonic of atherosclerosis.¹⁻³ Clinical⁴⁻⁶ and histopathological⁷⁻⁹ studies confirm the close correlation between extent of coronary artery calcification (CAC) and burden of atherosclerotic coronary disease. Epidemiological studies suggest the probability of future cardiac events is closely related to atherosclerotic disease burden.^{10,11} The extent of CAC may therefore portend cardiovascular risk.¹²

Electron-beam CT (EBCT) scanning is a noninvasive technology well suited for cardiac imaging. Rapid (100 ms) scan acquisition permits cardiac images with minimal motion artifact. To date, the greatest experience with its use has been assessment of CAC extent. Calculation of an Agatston score for the entire coronary tree provides a noninvasive, quantitative measure of CAC.¹³ In vitro experiments confirm the accuracy of EBCT in quantifying CAC.¹⁴ The estimated sensitivity and specificity of CAC on EBCT to detect $\geq 50\%$ stenosis at angiography are 97% and 72%, respectively.¹⁵

The clinical role of CAC quantification by EBCT is uncertain. This technique provides measurement of both atherosclerosis progression over time¹⁶ and the effects of pharmacological intervention.¹⁷ Evidence is also accumulating that CAC extent on EBCT may predict hard cardiac events in asymptomatic individuals.¹² However, only 1 study to date has examined its prognostic role in symptomatic patients undergoing coronary angiography.¹⁸ That study demonstrated that CAC quantification by EBCT was superior to angiographic measures of coronary artery disease (CAD) in predicting subsequent hard cardiac events (cardiac death or nonfatal myocardial infarction [MI]) during a mean follow-up period of 2.5 years. The study did not consider history of MI or revascularization in its patients. Thus, the prognostic potential of CAC extent compared with prior CAD event history (MI or revascularization) is not known. The association of CAC extent with subsequent hard cardiac events over a longer follow-up period is also uncertain.

Received January 4, 2001; revision received April 20, 2001; accepted April 20, 2001.

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To address these questions, we conducted a follow-up study of 317 patients who underwent both EBCT scanning and coronary angiography a mean of 6.9 years earlier. Any intercurrent history of cardiac death and nonfatal MI was determined to establish whether CAC extent at baseline correlated with future hard cardiac events. The role of CAC extent after consideration of selected CAD risk factors, prior CAD event history, and angiographic findings was also investigated.

Methods

A group of 317 white patients (71 women) underwent both coronary angiography and EBCT assessment within a 4-week period at our institution between 1989 and 1995. These patients were participants in a study designed to evaluate the association between EBCT measures of CAC and angiographic lumen stenosis. Clinically stable patients undergoing coronary angiography were invited to participate. The indication for angiography was evaluation of chest pain in 89% of cases. Patients were not selected for angiography on the basis of their EBCT examination results, and most had EBCT after angiography, usually the next day. The Institutional Review Board approved the protocol, and participating patients gave informed consent.

Coronary Angiography and EBCT

Coronary angiography was performed by the Judkins approach. Two angiographers visually assessed the extent of stenoses in each Coronary Artery Surgery Study (CASS) coronary segment.¹⁹ Information regarding disease extent within each coronary segment was therefore available in all cases. We considered a vessel diseased if any of its segments contained a stenosis $\geq 50\%$. Angiographic disease burden was calculated as the sum of stenoses in each CASS coronary segment.

EBCT studies were performed with an Imatron C-100 (Imatron Inc) scanner as described previously.^{13,20} After scan acquisition, an automated system was used to score the tomograms. Lesion area in square millimeters was recorded, and the peak CT density of each lesion was calculated. Multiplication of the measured area of any lesion $\geq 1.0 \text{ mm}^2$ by an attenuation coefficient based on its peak CT number generated a score for each lesion.¹³ Summation of the scores for each lesion in each coronary artery provided an overall calcium score. After the technical quality and scoring accuracy of each tomogram were inspected, an experienced radiologist interpreted the findings.

Cardiac Risk Factors and CAD Event History

Selected risk factors were abstracted from medical records at the time of hospital discharge. Data collected included age, sex, family history of premature CAD, smoking history, and diagnoses of hypertension and diabetes mellitus (defined as a fasting blood glucose $>140 \text{ mg/dL}$ or administration of insulin or oral hypoglycemic agents). Baseline cholesterol levels were missing in 28 patients (10%) and were not included in these analyses.

Additionally, information regarding CAD event history was collected. One hundred seven patients had a history of a cardiac event either before or concurrent with their index hospital admission. These events included MI or revascularization before admission ($n=25$), MI during the index admission ($n=28$), and myocardial revascularization during the index admission ($n=54$). History of MI before or during index hospital admission was included as a predictor, as was history of having revascularization without prior MI in the same time frame.

Follow-Up

Patients were questioned by 2 of the authors (P.C.K. and K.A.) during a telephone interview using a customized questionnaire a mean of 6.9 years (range 2.7 to 9.7 years) after initial evaluation. Any intervening history of MI was determined. If patients were

deceased, a death certificate was obtained. Cause of death was attributed to cardiac disease if the death certificate identified this as the principal cause of the patient's demise.

Statistical Analysis

CAC score and angiographic disease burden were natural logarithm transformed [$\log(\text{CAC score}+1)$ and $\log(\text{burden}+1)$] to reduce skewness. Patient characteristics among those with and without successful follow-up were compared. Among subjects with successful follow-up, patient characteristics were compared between those with and without subsequent hard events. Event-free survival for patients with CAC scores <100 and ≥ 100 were compared with Kaplan-Meier curves and log-rank tests.

Univariate Cox proportional hazards regression models were used to determine whether risk factors, CAD event history, CAC measures, and angiographic measures of CAD at index hospital admission predicted future hard events. Stepwise multivariable Cox proportional hazards regression models were used to determine independent predictors of future hard events among the same candidate variables. A significance level of 0.05 was used for all analyses.

Results

Follow-up information was obtained for 288 (91%) of the 317 patients. The mean (range) time between baseline hospital admission and follow-up interview was 6.9 years (2.7 to 9.7 years). Table 1 provides a comparison of baseline characteristics of individuals in whom follow-up was and was not successful. There were no statistically significant differences between the 2 groups in risk factors, CAC score, or angiographic measures of disease. Patients successfully followed up, however, had a significantly higher prevalence of CAC ($P<0.01$).

On average, the 22 patients who had hard events were significantly older and had more extensive CAC. These patients also had significantly higher mean overall angiographic disease burden and higher mean number of angiographically diseased vessels than the 266 patients who did not have hard events ($P<0.05$ for all; Table 2). The distribution of hard events by CAC score quartile established that 1 event occurred among patients in the lowest quartile (CAC score ≤ 12), whereas 5 events occurred in the second quartile (12.01 to 159.61), 9 occurred in the third quartile (159.62 to 621.58), and 7 occurred in the highest quartile of CAC score (≥ 621.59 ; $P=0.07$, χ^2 test for trends).

During follow-up, 71% of hard events occurred in patients with CAC score ≥ 100 (relative risk [RR] 3.20; 95% CI 1.17 to 8.71). Kaplan-Meier survival curves for hard events are presented for those with CAC scores ≥ 100 and <100 (Figure).

In univariate Cox proportional hazards models, age, log-transformed CAC score, log-transformed angiographic disease burden, and number of angiographically diseased vessels were all significantly associated with future hard events ($P<0.05$; Table 3). In stepwise Cox proportional hazards models considering the selected risk factors and CAD event history alone, age was the only independent predictor of future hard events (RR 2.15; 95% CI 1.35 to 3.45; Table 4). When CAC measures were added to this model, both age and transformed CAC score were independent predictors of future hard events ($P<0.05$). The risk ratios (95% CI) for a 1-SD

TABLE 1. Comparison of Baseline Characteristics Between Patients With and Without Completed Follow-Up

	Group Followed-Up (n=288)	Group Not Followed-Up (n=29)	P
Risk factors			
Age, y	56±11 (31–80)	52±12 (23–77)	0.053
Males, %	77	83	0.510
Hypertension, %	45	45	0.946
Diabetes, %	13	24	0.108
Family history of coronary disease, %	51	55	0.698
History of smoking, %	62	72	0.260
CAC			
Presence of CAC, %	89	72	0.009
CAC score	480±822	409±784	
Log (CAC score+1)	4.4±2.5	3.6±2.9	0.095
CAC score ≥100, %	57	48	0.351
Angiography			
Overall burden of disease	235±216	215±228	
Log (burden+1)	4.4±2.2	3.9±2.6	0.244
Number of vessels with ≥50% stenosis	1.3±1.2	1.2±1.2	0.725

Values are mean±SD (range) for continuous variables and percentage for categorical variables.

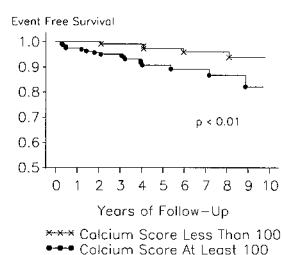
increase in age and log-transformed CAC score were 1.72 (1.02, 2.91) and 1.88 (1.02, 3.48), respectively (Table 4). When the selected risk factors, CAD event history, and angiographic measures of CAD were considered as possible predictors of future hard events, age was the only independent predictor of future hard events. Angiographic measures of

CAD failed to reach statistical significance. In the final stepwise Cox proportional hazards model that included risk factors, CAD event history, CAC measures, and angiographic measures of disease, age and log-transformed CAC score were the only independent predictors of future hard events (Table 4).

TABLE 2. Comparison of Baseline Characteristics Between Patients With and Without Subsequent Hard Events

	Hard Events (n=22)	No Hard Events (n=266)	P
Risk factors			
Age, y	61±11 (44–77)	56±11 (32–81)	0.048
Males, %	68	78	0.280
Hypertension, %	36	46	0.371
Diabetes, %	23	12	0.169
Family history of coronary disease, %	50	52	0.892
History of smoking, %	59	62	0.785
CAD event history			
MI before or during admission, %	5	17	0.120
Revascularization before or during admission, %	18	21	0.750
CAC			
Presence of CAC, %	95	89	0.327
CAC score	1077±1736	430±679	
Log (CAC score+1)	5.8±2.0	4.3±2.5	0.007
CAC score ≥100, %	77	56	0.049
Angiography			
Overall burden of disease	322±190	228±217	
Log (burden+1)	5.4±1.4	4.3±2.2	0.002
Number of vessels with ≥50% stenosis	1.9±1.0	1.2±1.2	0.024

Values are mean±SD (range) for continuous variables and percentage for categorical variables.



Kaplan-Meier survival curves for 123 patients with CAC score <100 (5 hard events) and 165 patients with CAC score \geq 100 (17 hard cardiac events). Patients with CAC scores \geq 100 had significantly poorer outcome than patients with scores <100 ($P<0.01$).

Discussion

A recent scientific statement on CAC issued by the American Heart Association identified the necessity for data collection about future cardiac events to determine its clinical significance.²¹ To date, most studies addressing the association of CAC with future events have been conducted in asymptomatic individuals.^{22–24} In a recent meta-analysis, an increased risk for hard events was noted with a summary risk ratio of 4.2 (95% CI 1.6 to 11.3) if the CAC score was above the median.¹² Interestingly, in the present study of predominantly symptomatic individuals, we observed a similar risk ratio (3.4; 95% CI 1.3 to 8.7) for hard events if the CAC score was above the median.

Only 2 published studies have addressed the impact of CAC in symptomatic individuals, and only 1 of these studies used EBCT. Margolis and colleagues²⁵ used fluoroscopy to

TABLE 3. Unadjusted RR of Hard Cardiac Event as a Function of Risk Factors, CAD Event History, CAC, and Angiographic Results

	Unadjusted RR* (95% CI)	P
Risk factors		
Age	2.15 (1.35,3.45)	0.001
Male sex	0.52 (0.21,1.28)	0.155
Hypertension	0.73 (0.31,1.74)	0.475
Diabetes	2.11 (0.78,5.73)	0.141
Family history of coronary disease	0.96 (0.42,2.21)	0.921
History of smoking	0.82 (0.35,1.93)	0.650
CAD event history		
MI before or during admission	0.23 (0.03,1.69)	0.147
Revascularization before or during admission	0.96 (0.32,2.84)	0.938
CAC		
Presence of CAC	2.83 (0.38, 21.05)	0.310
Log (CAC score+1)	2.44 (1.35,4.40)	0.003
CAC score \geq 100	3.2 (1.17,8.71)	0.023
Angiography		
Log (Burden+1)	2.55 (1.19,5.45)	0.016
Number of vessels with \geq 50% stenosis	1.58 (1.11,2.23)	0.010

*For 1-SD increase in continuous variables.

TABLE 4. Stepwise Multivariable Cox Proportional Hazards Regression Models for Survival Free of Hard Events With Risk Factors, CAD Event History, CAC, and Angiographic Results

	RR* 95% CI	P
Risk factors and CAD event history		
Age	2.15 (1.35, 3.45)	0.001
Risk factors, CAD event history, and CAC		
Age	1.72 (1.02, 2.91)	0.043
Log (CAC score+1)	1.88 (1.02, 3.48)	0.044
Risk factors, CAD event history, and angiographic results		
Age	2.15 (1.35, 3.45)	0.001
Risk factors, CAD event history, angiographic results, and CAC		
Age	1.72 (1.02, 2.91)	0.043
Log (CAC score+1)	1.88 (1.02, 3.48)	0.044

*For 1-SD increase in continuous variables.

evaluate 800 patients referred for angiography. They noted an increased 5-year mortality rate in subjects with CAC compared with those without CAC (87% and 58%, respectively). This association was independent of age, sex, and number of angiographically diseased vessels. Fluoroscopy, however, cannot provide accurate quantification of CAC.

Detrano and colleagues¹⁸ published results of a multicenter trial examining the prognostic value of CAC detected by EBCT for predicting hard cardiac events in 491 patients undergoing angiography. Follow-up was completed in 86% of the patients a mean of 30 months after baseline examination. In all, 21 hard events (13 cardiac deaths and 8 nonfatal MIs) occurred during follow-up, and event frequency increased significantly across ascending quartiles of CAC score. In the present study, the trend in frequency of events across ascending quartiles just failed to reach statistical significance ($P=0.07$). In the Detrano study, the CAC score emerged as the only independent predictor of events after application of stepwise logistic regression. Age, sex, and number of angiographically diseased vessels were not significantly associated with hard events.

The present study confirms the previous findings of Detrano et al¹⁸ that CAC extent determined by EBCT provides more prognostic information than angiography in symptomatic patients. There are several important differences, however, between the studies. Follow-up in the present study was longer (mean 6.9 years versus 2.5 years) and more complete (90.9% versus 84.8%). The median score of 159.6 was substantially higher than the median of 75.3 in the study by Detrano et al.¹⁸ We also included information about patients' risk factor profile and prior CAD event history.

In the present study, no conventional coronary risk factors other than age predicted events, although measures of cholesterol levels at baseline were not available for 28 patients. Surprisingly, a history of MI or revascularization before or during index hospitalization was not associated with an increased likelihood of subsequent hard events. The benefits of aggressive risk factor modification and revascularization

techniques provided to patients seen in this tertiary referral center might explain this observation.

Aside from increasing age, CAC extent on EBCT was the most powerful predictor of subsequent hard events in the present study. This suggests that more can be inferred about subsequent cardiac risk from quantification of CAC extent than from a coronary angiogram in patients similar to those in the present study. These results cannot be extended to asymptomatic patients, however.

Future hard events were very rare in patients with minimal calcification, even though the clinical suspicion for CAD in these patients was sufficient to warrant angiography. During a mean follow-up period of almost 7 years, only 1 of the 87 patients in this cohort with a CAC score <20 experienced a hard event (this patient also had a normal coronary angiogram). The close correlation between mural calcification and plaque burden accounts for the protective effect of a low CAC score.

It is widely believed that the existence of vulnerable plaque, the predominant pathological substrate of hard cardiac events, is closely related to CAD extent. Several studies have confirmed that disease burden is highly correlated with subsequent cardiac death and MI.^{10,11}

Histological studies demonstrate a strong correlation between the extent of vessel calcification and overall plaque burden.^{7,8} This association is unaffected by the remodeling phenomenon, which entails vessel wall enlargement to compensate for increasing plaque volume.²⁶ As the overall disease burden and the likelihood of vulnerable plaque increase, so does CAC extent.²⁷

Although regarded as the "gold standard" investigation for identification of CAD, the angiogram provides no information on plaque burden other than the extent of luminal obstruction. The remodeling phenomenon results in a disparity between plaque burden and angiographic stenosis.²⁸ This limits the information that may be gleaned from a coronary angiogram regarding disease burden and the likelihood of vulnerable plaque.²⁹

Therefore, in patients with a minimally abnormal coronary angiogram, the physician may erroneously conclude that the overall disease burden is mild. In this patient subset, an EBCT scan demonstrating considerable calcification may add important prognostic information and identify the need for aggressive medical therapy and regular patient follow-up.

Study Limitations

This is a retrospective study in a cohort of patients who underwent EBCT scanning at the time of coronary angiography to evaluate the association between CAC score and angiographic disease. The end points presented here were not identified prospectively. We do not believe that patients with higher CAC scores received more aggressive therapy (surveillance bias), because no clinical role for the CAC score had been identified at the time of the study, and primary physicians were typically unaware of the result. However, selection bias cannot be excluded in this study, because enrollment into the study was not consecutive.

Cholesterol levels were not available in 10% of this cohort. Patients with missing cholesterol data were more likely to be

older (60.9 versus 55.7 years, $P=0.02$). No other significant differences in CAD risk factor profile, CAD event history, CAC score, angiographic disease, or future hard events were noted between those with and without measured cholesterol. Among the 260 patients with cholesterol measures, cholesterol was not a significant predictor of future hard events in univariate or multivariate analysis. In this smaller group of patients, CAC score remained a significant predictor of future hard events in multivariable models, whereas angiographic measures of CAD failed to reach significance.

In summary, this study presents strong evidence that CAC extent provides important prognostic information in patients with indications for coronary angiography. Quantification of CAC extent by EBCT was superior to coronary angiographic findings in predicting future hard events over almost 7 years in these symptomatic patients. When available, this test should be considered in all patients with indications for angiography. As the CAC score increases, so does the patient's risk of future hard events independent of age, other CAD risk factors, CAD event history, or angiographic findings.

Acknowledgment

This study was supported in part by National Institutes of Health grant HL-46292.

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Circulation. 2001;104:412-417
doi: 10.1161/hc2901.093112

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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