Prognostic Value of Coronary Calcification and Angiographic Stenoses in Patients Undergoing Coronary Angiography

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Objectives. **This investigation sought to determine the relative prognostic value of coronary calcific deposits and coronary angiographic findings for predicting coronary heart disease-related events in patients referred for angiography.**

Background. **The relation among coronary calcification, coronary stenoses and coronary heart disease-related events is of interest on a clinical as well as a pathophysiologic basis.**

Methods. **Four hundred ninety-one symptomatic patients underwent coronary angiography and electron beam computed tomography at five different centers between April 1989 and December 1993. The electron beam computed tomograms were interpreted by a cardiologist with no knowledge of the coronary angiographic and clinical data. Receiver operating characteristic (ROC) curves were constructed to determine the relation between electron beam computed tomographic and coronary angiographic findings. A follow-up telephone survey was completed in 86% of patients. The records for all patients who died or were admitted to the hospital for chest pain or suspected myocardial infarction were reviewed by three other cardiologists with no knowledge of the coronary angiographic and electron beam computed tomographic study results.**

Results. **The mean (±SE) area under the ROC curve was 0.75 ± 0.02 for the coronary calcium score, indicating moderate discriminatory power for this score for predicting angiographic findings. Thirteen coronary heart disease-related deaths and eight nonfatal acute infarctions occurred over 30 ± 13 months. Scores were sorted in ascending order and divided into quartiles of equal size. One patient in the first quartile had a fatal myocardial infarction (coronary calcium score range 0 to 2.1); 2 in the second quartile (range 2.1 to 75.3), 8 in the third quartile (range 75.3 to 397.1) and 10 in the fourth quartile (>397.1) had a coronary heart disease-related event. Application of bivariate logistic regression showed that log score but not number of angiographically diseased vessels significantly predicted the probability of a coronary heart disease-related event occurring during follow-up.**

Conclusions. **Electron beam computed tomographic calcium scores correlate moderately well with angiographic findings. These scores predict coronary heart disease-related events in patients undergoing angiography as well as do the number of angiographically affected arteries.**

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Coronary atherosclerosis is a leading cause of death and disability in the United States. Recently, there has been interest in electron beam computed tomography to diagnose early coronary atherosclerosis (1–4). Pathology studies have shown a correlation between coronary atherosclerosis and coronary calcification (5,6) as detected by electron beam tomography, and initial angiographic studies have shown that calcifications in the coronary artery tree reasonably predict stenoses in the same tree, although not necessarily at the same anatomic site (7,8).

The aims of the investigation reported herein were to assess the relation of coronary calcifications and angiographic stenoses and the relative contribution of both of these to future coronary heart disease-related events in symptomatic patients referred for angiography.

Methods

Patient selection. This comparative multicenter study involved 491 symptomatic patients who underwent coronary angiography and electron beam computed tomography at five different medical centers between April 1989 and December 1993 and who fulfilled the following inclusion criteria: 1) All computed tomographic studies were done within 3 months of

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coronary angiography; 2) all computed tomographic studies utilized either the 26-, 30- or 34-cm reconstruction field of view; 3) all reconstructed image data could be retrieved by personnel at the participating centers and transported to the reading center; 4) all patients were discharged alive from the hospital after their coronary angiogram. One patient who died during the index hospital period was excluded.

Eighty-eight patients who did not fulfill at least one of these criteria were excluded. Participating centers included the State University of New York at Buffalo, New York; the Shields Cine CT Center in Spokane, Washington; the University of Iowa in Iowa City, Iowa; the University of Illinois Medical Center in Chicago, Illinois; and the Harbor-UCLA Medical Center in Los Angeles, California. Patients were selected for coronary angiography at the five centers on the basis of clinical indications including but not exclusive to angina or myocardial infarction. Computed tomographic scanning was performed in most cases as part of clinical research studies, and scan results did not generally influence the decision to perform coronary angiography. All patients contacted for follow-up by telephone gave informed consent, and the follow-up protocol was approved by the Harbor-UCLA Human Subjects Committee in February 1994.

Coronary angiography. Angiographic studies were each analyzed by experienced readers who evaluated the presence of significant angiographic obstructions in each of the four major epicardial vessels. The angiograms were read by caliper-assisted visual approximation of lumen reduction in each coronary vessel (left main, left anterior descending, circumflex and right coronary artery). Vessels with >50% lumen diameter stenosis were deemed significantly diseased. Patients with disease in the left main coronary artery were treated as having three diseased vessels regardless of whether or not other epicardial arteries were affected. In three of the centers, angiograms were reinterpreted by a second observer, also in a blinded manner. There was agreement in categorization of patients as to the presence of disease in >95% of the angiograms done at these centers.

Electron beam computed tomography. The electron beam computed tomographic studies were performed with an Imatron C-100 computed tomographic scanner using a high resolution volume mode with 100-ms exposure time. Between 20 and 40 3-mm image slices were acquired for each patient study.

Reconstructed image studies were transferred to digital optical disks at the five centers. These disks were transported to the Los Angeles reading center, and the image studies were electronically transferred to a workstation. The software of this workstation includes an interactive three-dimensional image analysis system that was designed specifically to assess calcification in electron beam computed tomographic images (9). A cardiologist with experience in both coronary angiography and cardiac computed tomographic analysis (S.W.) used this system to score the extent of calcification in each scan. This observer had no knowledge of the clinical or angiographic data. The software system used, whose accuracy has been verified (9–12), embodies an analysis protocol with the following steps. The cardiologist identified the three-dimensional arterial midlines and tomographic planes. The software then extracted cylindrical regions of interest with radii of 6 mm surrounding these midlines. The cardiologist could edit these regions of interest to include omitted segments or exclude noncoronary calcification. The system searched the interiors of these regions and identified all foci with an area of at least 1 mm^2, all of whose pixel values exceeded a threshold value of 130 Hounsfield units (HU). The system calculated the Agatston calcium score (13) of each focus of calcification within the regions created and summed these for each artery and for the entire heart.

Sixty-seven of these image studies were also analyzed in blinded manner using the standard scanner-supplied software by another cardiologist with experience in reading electron beam computed tomographic results (R.D.). Analysis of this subsample showed insignificant differences between the work station and the scanner software results when those interpreting the studies using both methods had no knowledge of the angiographic findings (12). Interobserver differences were also found to be equivalent to those of the scanner software (12).

Prognostic follow-up. The research staff in Los Angeles conducted a telephone survey of the 491 patients with available computed tomographic images. If patients were deceased, telephone interviews were conducted with a relative. Patients were asked if they had been admitted to a hospital since their electron beam computed tomographic study. Medical records were obtained for all admissions where death had occurred or when the presenting complaint had been chest pain or dyspnea, or when the patient claimed that the discharge diagnosis had been cardiac related. Records obtained included electrocardiograms, creatine kinase-MB fractions and clinical discharge summaries. All deaths were confirmed with death certificates, medical records or conversations with personal physicians. When death had occurred at home, a staff member transcribed a conversation with a family member. This conversation included questions regarding the circumstances of death and the presence of chest pain before death. Three board-certified cardiologists who were unaware of the coronary angiographic and computed tomographic results reviewed these records of hospital admissions and conversations with family members. The cardiologists were then asked to decide whether an acute myocardial infarction or coronary heart disease-related death had occurred.

Statistical analysis. Because of the nonnormality of coronary calcium scores, base-10 log plus 1 $\log_{10}(x + 1)$ transformations were made for all statistical calculations. Sensitivities and false positive rates for predicting a >50% angiographic stenosis were calculated for all possible threshold calcium scores. These were plotted in receiver operating characteristic (ROC) space, and the area under the curve was calculated using the trapezoid rule (14). Coronary calcium scores were sorted in ascending order and then divided into equal-sized quartiles. The number of coronary heart disease-related events (coronary-related deaths and myocardial infarctions) occurring in each quartile were determined and compared using the

Table 1. Demographic, Angiographic and Electron Beam Computed Tomographic Information by Site

Center	No. of Patients	Mean ± SD Age (yr)	Percent Men	Percent With Angiographic Disease	Mean ± SD Score	Percent With Calcium	No. of Events
Buffalo	139	49 ± 11	60	27	153 ± 300	71	1
Los Angeles	67	55 ± 10	48	34	376 ± 777	82	2
Chicago	96	56 ± 13	45	44	418 ± 820	82	5
Iowa City	81	60 ± 13	56	42	329 ± 704	74	6
Spokane	108	60 ± 10	72	69	482 ± 679	93	7
Overall	491	55 ± 12	57	43	336 ± 659	80	21

chi-square test for trends. Chi-square analysis and analysis of variance were used to compare discrete and continuous variables among centers, between age-sorted and gender-sorted groups, and between successful and unsuccessful follow-up.

Logistic regression was used to determine the independent relative contributions of the angiographic and computed tomographic findings. We required at least 10 end points per independent variable to obtain a stable multivariate logistic model. In an additional multivariable calculation, we controlled for age and gender by allowing age, gender, angiographic results and calcium score to be candidate variables in a stepwise logistic regression that would choose no more than the two most significant predictors of events.

Survival and event-free survival curves were created for subjects with calcium scores <100 and ≥100. Similar curves were created and compared for those with and without a >50% lumen narrowing by coronary angiography. These were compared using the Wilcoxon test.

Results

There were 491 patients who fulfilled the four inclusion criteria (280 men [57%]; 211 women [41%]; mean [±SD] age 55 ± 12 years, range 24 to 85). Table 1 shows the demographics of these patients by the center at which they underwent coronary angiography. These data were heterogeneous in that the number of women was highest in Chicago ($p = 0.0001$), and the mean age was significantly lower in Buffalo ($p = 0.0001$).

Results of electron beam computed tomography and coronary angiography. The mean log calcium score in the 491 patients was 1.61 ± 1.13. Of the 491 patients, 211 (43%) were observed to have angiographically significant disease, characterized as >50% minimal lumen diameter stenosis in any major epicardial vessel. The mean log score in the 211 patients with significant angiographic disease was 2.18 ± 0.?1, and 1.17 ± 1.08 in those without angiographic disease ($p = 0.0001$). Table 1 also shows the prevalences of angiographic disease and mean calcium scores in the five centers. The distribution of events and scores was heterogeneous in the five centers ($p < 0.003$, chi-square and analysis of variance). Both of these were lower in Buffalo than in the other centers.

Diagnosis. The overall sensitivity for predicting significant angiographic disease was 95% when any calcification (score >0) was used as as a criterion for abnormal scan results. The specificity using this criterion was 31%. The sensitivity was 70% and the specificity 71% when a threshold score of 100 was used to define abnormal study findings. The ROC curve shown in Figure 1 illustrates the overall discriminatory power of this test for diagnosing angiographic coronary artery disease. The area under the curve is 0.75 ± 0.02. Table 2 shows the sensitivity and specificity of coronary calcification in men and women and in patients >55 and ≤55 years of age. Coronary calcium is more specific for angiographic stenoses in younger patients and in female patients.

Prognosis. The research staff successfully obtained follow-up data for 422 (86%) of the cohort of 491 patients. There were no differences in coronary calcium score or number of angiographically diseased vessels between patients with and without available follow-up data. Those lost to follow-up were significantly younger (mean age 52) than those with available follow-up data (mean age 56, $p = 0.02$).

Thirty-eight patients died during a follow-up period of 30 ± 13 months. There were a total of 21 coronary heart disease-related events. Thirteen of these were coronary heart disease-related deaths: 12 were from sudden cardiac death, and 1 from myocardial infarction. There were eight nonfatal myocardial infarctions. Table 1 shows the distribution of events by center. Table 3 shows the distribution of events and all-cause deaths by quartile of coronary calcium score. Both events and deaths

Figure 1. Receiver operator characteristic curve for coronary calcium score. **Solid arrow** = point for threshold score of zero (any calcification); **dashed arrow** = point for threshold score of 100.

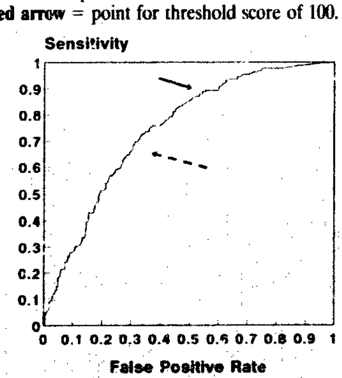

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Table 2. Sensitivity and Specificity Related to Gender and Age

	Any Detectable Calcium		Score >100	
	Sensitivity	Specificity	Sensitivity	Specificity
Men				
Age >55 yr (127, 74)	97%	13%	86%	51%
Age ≤55 yr (154, 75)	92%	30%	49%	73%
Women				
Age >55 yr (121, 47)	98%	31%	77%	65%
Age ≤55 yr (89, 15)	93%	46%	60%	88%

Numbers in parentheses are the number in each category followed by the number with angiographic disease.

tended to be more frequent in the higher quartiles ($p < 0.04$, chi-square for trends). The coronary heart disease event-free survival curves for subjects with calcium scores <100 and ≥100 are shown in Figure 2. These curves show the percentages of remaining subjects who had neither an infarction nor coronary heart disease-related death as a function of months of follow-up. Coronary event-free survival was significantly higher for patients with lower scores. Similar curves are shown for all-cause death in Figure 3. Figures 4 and 5 show event-free survival and all-cause survival curves for patients with and without >50% lumen obstruction. All pairs of curves were significantly different according to the Wilcoxon test.

Mean log calcium scores were higher in patients with (2.32 ± 0.94) than without events (1.58 ± 1.13) ($p = 0.004$). The quartile calcium score distribution for events demonstrated that 1 event occurred in the first quartile, where calcium scores fall between zero and 2.1; 2 events occurred in the second quartile, where calcium scores fall between 2.1 and 75.3; 8 occurred in the third quartile, with scores between 75.3 and 397.1, and 10 occurred in the fourth quartile, with scores above 397.1. This trend toward higher scores was significant by chi-square test for trends ($p = 0.03$).

Logistic regression, including number of angiographically diseased vessels and log calcium score, resulted in the following expression for the probability P of a coronary heart disease event during follow-up:

$$P = \exp(y)/[1 + \exp(y)];$$

$$y = 4.33 + 0.34^{**}\ (\text{number of vessels}) + 0.52^{*}\ (\text{log score});$$

$$^{*}p = 0.05; \quad ^{**}p = 0.11.$$

Table 3. Number of Events in Each Quartile of Coronary Calcium Scores

Quartile of Score	Range of Scores	No. of Events	No. of Deaths
1	0–2.1	1	3
2	2.1–75.3	2	4
3	75.3–397.1	8	9
4	>397.1	10	22

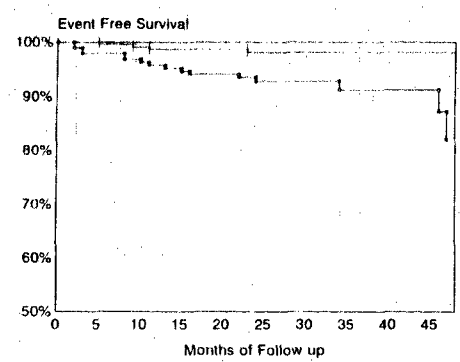


Figure 2. Coronary heart disease event-free survival distribution for patients with calcium scores <100 **(upper curve)** and ≥100 **(lower curve)**. Curves are significantly different ($p = 0.009$, Wilcoxon test).

Application of stepwise logistic regression, including age, gender, log score and number of angiographically affected vessels, resulted in only log score as an independent predictor of events. This relation was

$$P = \exp(y)/[1 + \exp(y)];$$

$$y = 4.33 + 0.68^{*}\ (\text{log score});$$

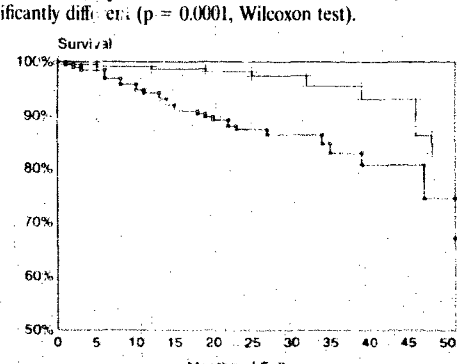
$$^{*}p = 0.006.$$

Thus, the contribution of log calcium score to prognosis remained significant after adjustment for number of angiographically diseased vessels as well as for age and gender.

Discussion

The results of the present investigation support the contention that electron beam computed tomographic coronary calcium scores correlate only moderately well with angiographic findings. Other studies using blinded readings of coronary calcium findings arrived at similar conclusions (7,8). Studies not using blinded readings (15) resulted in test review bias

Figure 3. All-cause survival distribution for patients with calcium scores <100 **(upper curve)** and ≥100 **(lower curve)**. Curves are significantly different ($p = 0.0001$, Wilcoxon test).



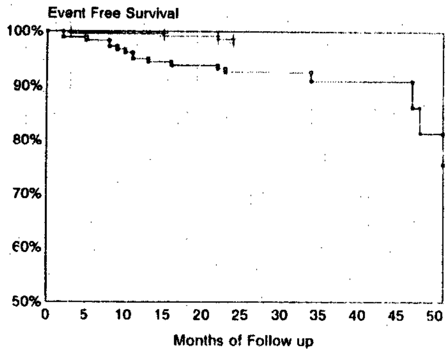


Figure 4. Coronary heart disease event-free survival distribution for patients with (**lower curve**) and without (**upper curve**) >50% angiographic stenosis. Curves are significantly different (p = 0.002, Wilcoxon test).

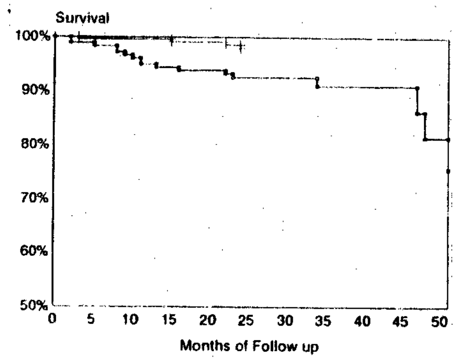


Figure 5. All-cause survival distribution for patients with (**lower curve**) and without (**upper curve**) >50% angiographic stenosis. Curves are significantly different (p = 0.006, Wilcoxon test).

(16,17), causing stronger associations with angiographic findings. The ROC area derived from integrating under the curve in Figure 1 was 0.75, which compares well with those found for exercise electrocardiography (18) and suggests that computed tomographic detection of coronary calcium is equivalent to exercise electrocardiography in its ability to detect angiographic coronary artery disease in symptomatic patients.

A primary and important finding of the present investigation is the strong association between the electron beam computed tomographic findings and coronary heart disease-related events. Patients with a coronary calcium score higher than the median (75.3, corresponding to a calcium hydroxyapatite load of ~30 mg [19]) were six times as likely to have a coronary heart disease-related event as those with a score below the median. Because of the small number of events, stable multivariable regression calculations including many variables could not be executed. However, a logistic regression model for predicting the probability of an event and including log score and number of angiographically affected vessels resulted in a statistically significant effect for log score. This suggests that coronary calcium amount contributes independent information toward the probability of atherosclerotic plaque rupture and subsequent events. Margolis et al. (20) found that patients with fluoroscopically detected coronary calcium who were undergoing angiography were four times more likely to die in an 8-year follow-up period than were those without coronary calcium. Those investigators found that coronary calcium was a stronger predictor of prognosis than the angiographic findings. Thus, the results of this early fluoroscopic investigation are consistent with the results reported here.

Coronary calcium and stenoses are different manifestations of atherosclerosis. The former has been found to have a fair correlation with the volume of plaque in studies of postmortem specimens (21–23). The relation between stenosis and plaque volume, however, is complex. Percent diameter stenosis depends heavily on the diameters of the reference segments assumed to be normal and on the compensatory enlargement of both index and reference segments (24). This compensatory enlargement causes the angiographic coronary lumina to contract at a rate slower than the rate at which the plaque volume grows. A greater volume of plaque, much of which is calcified, probably increases the risk of plaque rupture. Therefore, remodeling of the coronary arteries decreases the importance of stenoses and increases that of calcification in the prediction of plaque rupture and its clinical consequences.

Demer (25) has postulated that calcification may actively contribute to the susceptibility of plaque rupture and subsequent events. Her experiments in atherosclerotic rabbit aortas showed that these vessels were more likely to rupture when they were calcified. Such a mechanistic link would help explain the prognostic value of coronary calcifications. Whatever the mechanism, our results support the use of this technology for risk stratification in the symptomatic patient with known or suspected coronary artery disease.

Limitations and reservations. Most investigators (7,8, 13,15,18,26–29) utilize visual analysis of coronary angiographic images when applying angiography as a reference standard for evaluating a noninvasive diagnostic test. Although we also analyzed our angiograms using a caliper-assisted visual assessment, we are aware of the pitfalls of this approach (30). Even quantitative coronary angiography does not correlate perfectly with functional assessments (31), and invasive physiologic measurements (32) or intravascular ultrasound assessments would be a more ideal reference standard.

Clinical application. Margolis et al. (20) have shown that fluoroscopic calcifications are also predictive of coronary end points in patients undergoing angiography. Because fluoroscopic results are available at the time of angiography, we cannot recommend the clinical application of an additional test (electron beam computed tomography) for all those undergoing an angiographic examination. However, the important prognostic information provided may be of assistance in precluding the performance of angiography when calcium is absent and in hastening its performance when calcium is abundant.

Conclusions. The results reported here do not mean that electron beam computed tomographic coronary calcium testing is a valid screening test for asymptomatic subjects. The very high prevalence of coronary calcifications in such subjects and the uncertainty as to an applicable threshold of calcium quantity (33) suggest that the clinical application of electron beam computed tomographic screening should be restricted to the evaluation of symptomatic patients only.

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