Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 49, No. 18, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.10.079



# Long-Term Prognosis Associated With Coronary Calcification

## Observations From a Registry of 25,253 Patients

Matthew J. Budoff, MD,* Leslee J. Shaw, PHD,† Sandy T. Liu,* Steven R. Weinstein,* Tristen P. Mosler, Philip H. Tseng,* Ferdinand R. Flores,* Tracy Q. Callister, MD,‡ Paolo Raggi, MD,§ Daniel S. Berman, MD†

*Torrance and Los Angeles, California; Nashville, Tennessee; and Atlanta, Georgia*

**Objectives** The purpose of this study was to develop risk-adjusted multivariable models that include risk factors and coronary artery calcium (CAC) scores measured with electron-beam tomography in asymptomatic patients for the prediction of all-cause mortality.

**Background** Several smaller studies have documented the efficacy of CAC testing for assessment of cardiovascular risk. Larger studies with longer follow-up will lend strength to the hypothesis that CAC testing will improve outcomes, cost-effectiveness, and safety of primary prevention efforts.

**Methods** We used an observational outcome study of a cohort of 25,253 consecutive, asymptomatic individuals referred by their primary physician for CAC scanning to assess cardiovascular risk. Multivariable Cox proportional hazards models were developed to predict all-cause mortality. Risk-adjusted models incorporated traditional risk factors for coronary disease and CAC scores.

**Results** The frequency of CAC scores was 44%, 14%, 20%, 13%, 6%, and 4% for scores of 0, 1 to 10, 11 to 100, 101 to 400, 401 to 1,000, and >1,000, respectively. During a mean follow-up of 6.8 ± 3 years, the death rate was 2% (510 deaths). The CAC was an independent predictor of mortality in a multivariable model controlling for age, gender, ethnicity, and cardiac risk factors (model chi-square = 2,017, $p < 0.0001$). The addition of CAC to traditional risk factors increased the concordance index significantly (0.61 for risk factors vs. 0.81 for the CAC score, $p < 0.0001$). Risk-adjusted relative risk ratios for CAC were 2.2-, 4.5-, 6.4-, 9.2-, 10.4-, and 12.5-fold for scores of 11 to 100, 101 to 299, 300 to 399, 400 to 699, 700 to 999, and >1,000, respectively ($p < 0.0001$), when compared with a score of 0. Ten-year survival (after adjustment for risk factors, including age) was 99.4% for a CAC score of 0 and worsened to 87.8% for a score of >1,000 ($p < 0.0001$).

**Conclusions** This large observational data series shows that CAC provides independent incremental information in addition to traditional risk factors in the prediction of all-cause mortality. (J Am Coll Cardiol 2007;49:1860–70) © 2007 by the American College of Cardiology Foundation

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Evidence-based guidelines recommend that primary care physicians make a careful assessment of their patients' baseline coronary heart disease (CHD) risk and focus primary prevention interventions (such as use of cholesterol-lowering drugs [1] and aspirin [2]) on intermediate- and high-risk patients. Standard risk factor analyses can help stratify patients into risk groups but are somewhat imprecise and leave a large proportion of patients classifiable as "intermediate" risk, a rather undetermined state. Cholesterol therapy of patients in this category might range from no therapy to a low-density lipoprotein target <100 mg/dl. More effective assessment of CHD risk might improve the outcome, cost-effectiveness, and safety of primary prevention efforts. We attempted to assess the prognostic power of coronary artery calcium (CAC) assessed with electron beam tomography (EBT). The purpose of this study was to develop long-term risk-adjusted multivariable predictive models to estimate death from all-causes, using cardiac risk factors and CAC scores determined with EBT.

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From the *Harbor-UCLA Los Angeles Biomedical Research Institute, Torrance, California; †Cedars-Sinai Medical Center, Los Angeles, California; ‡EBT Research Foundation, Nashville, Tennessee; and the §Division of Cardiology and Department of Radiology, Emory University, Atlanta, Georgia. Dr. Budoff is on the speakers' bureau for General Electric.

Manuscript received March 6, 2006; revised manuscript received September 18, 2006, accepted October 16, 2006.

## Methods

**Patient entry criteria.** The study sample consisted of 25,253 consecutive asymptomatic individuals referred by primary physician for CAC measurement with EBT. Subjects were given a risk-factor questionnaire to assess ethnicity and cardiovascular risk factors. The presence and number of risk factors for a subject was calculated on the basis of the National Cholesterol Education Program guidelines (1). Risk factors included: age (men >45 years, women >55 years), current cigarette smoking, diabetes, history of premature coronary disease in first-degree relative (men <55 years, women <65 years), hypertension, and hypercholesterolemia. Current cigarette smoking was defined as any cigarette smoking in the past month. Hypertension was defined by current use of anti-hypertensive medication or known and untreated hypertension. Hypercholesterolemia was defined as use of cholesterol lowering medication or, in the absence of cholesterol lowering medication use, as having a total serum cholesterol >200 mg/dl. Total cholesterol measurements were available in 11,275 subjects and were categorized as <200, 201 to 240, 241 to 260, and >260 mg/dl, respectively. Patients also noted whether they were taking statin therapy at the time of scanning.

**EBT methods.** All study subjects underwent EBT with an Imatron C-150XL Ultrafast computed tomography scanner (GE-Imatron, South San Francisco, California). The study was approved by the Institutional Review Board of Harbor-UCLA Medical Center. Thirty to 40 contiguous tomographic slices were obtained at 3-mm intervals beginning 1 cm below the carina and progressing caudally to include the entire coronary tree. Exposure time was 100 ms/tomographic slice, and total irradiation dose was 0.6 mSv/scan.

An attenuation threshold of 130 HU and a minimum of 3 contiguous pixels were used for identification of a calcific lesion. Each focus exceeding the minimum criteria was scored with the algorithm developed by Agatston et al. (3), calculated by multiplying the lesion area by a density factor derived from the maximal HU within this area. The density factor was assigned in the following manner: 1 for lesions with peak attenuation of 130 to 199 HU, 2 for lesions with peak attenuation of 200 to 299 HU, 3 for lesions with peak attenuation of 300 to 399 HU, and 4 for lesions with peak attenuation >400 HU. The total CAC score was determined by summing individual lesion scores from each of 4 anatomic sites (left main, left anterior descending, circumflex, and right coronary arteries) (3).

**Follow-up data collection.** Epidemiologic methods for follow-up included ascertainment of death by individuals who were blinded to historical and CAC score results (4,5). The occurrence of all-cause death was verified with the National Death Index (6). Individuals who underwent cardiovascular screening were followed for a mean of 6.8 years (SEM = 0.019) and median of 5.8 years (25th to 75th percentile = 4.7 to 8.9 years). Follow-up was completed in 100% of patients. In this sample, 5,218 patients had follow-up ≥10 years and 1,404 patients had follow-up ≥12 years.

**Data validation in a prior 10,377 patient series.** We compared our survival analysis with a similar referral population from patients enrolled in a prior registry (7,8) to examine near-term (3- to 5-year) versus long-term (7- to 10-year) survival. We pooled both datasets for validation of our mortality model in the current 25,253 patient series and the previously reported data in 10,377 patients.

**Abbreviations and Acronyms**

CAC = coronary artery calcium
CAD = coronary artery disease
CHD = coronary heart disease
CI = confidence interval
EBT = electron beam tomography
ROC = receiver-operating characteristic
RR = risk ratio

**Statistical methods.** We presented continuous measures as mean ± SD and frequency data as proportions. Categorical variables comparing CAC patient subsets with historical variables were compared with a chi-square likelihood ratio test. For comparing CAC subsets by age and other continuous measures, we employed analysis of variance techniques. A p value $< 0.05$ was considered statistically significant.

Time to death from all causes was estimated with a Cox proportional hazards model. Unadjusted survival and risk-adjusted survival rates controlling for age, gender, ethnicity, and other cardiac risk factors, detailed in Table 1, were calculated. For all variables in a model, univariable and risk-adjusted relative risk ratios (RRs) with 95% confidence intervals (CIs) were calculated.

Receiver-operating characteristic (ROC) curves were calculated, including a comparative analysis of age and other cardiac risk factors (Table 1) versus the CAC score. From the ROC curves, a concordance (or C-) index, a measure of event and non-event correct classification, was calculated including 95% CIs. In our first ROC curve analysis, we evaluated the area under the curve for age and other risk factors as compared with the continuous CAC score. Two ROC curves are presented, including model 1: comparing the number of cardiac risk factors with the continuous CAC score, and model 2: comparing age with the continuous CAC score.

We then evaluated multivariable or risk-adjusted Cox models with the CAC score in several coding schemes: 1) model 1: total CAC score using categories of 0, 1 to 10, 11 to 100, 101 to 400, 401 to 699, 700 to 999, and ≥1,000; and 2) model 2: dividing the arterial segment analysis of the CAC score into 0 to 3 vessels with CAC score ≥100. In particular, for each of these models, we calculated unadjusted analyses as well as age-adjusted and other risk-factor-adjusted (Table 1) survival models. From the multivariable models, we evaluated the added value of the CAC score by calculating a C-index and 95% CIs. As well, we calculated the Delta chi-square, a measure of the risk predictive content of a given variable within a multivariable model.

**Table 1** Overall Clinical Characteristics of the Study Population by Coronary Calcium Patient Subsets

| | | CAC Score | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Overall (n = 25,253) | 0 (n = 11,046) | 1–10 (n = 3,567) | 11–100 (n = 5,033) | 101–299 (n = 2,616) | 300–399 (n = 561) | 400–699 (n = 955) | 700–999 (n = 514) | ≥1,000 (n = 965) | p Value |
| Average score | 146 ± 443 | 0 ± 0 | 4 ± 3 | 44 ± 26 | 176 ± 56 | 349 ± 30 | 528 ± 84 | 836 ± 84 | 1,935 ± 1,057 | <0.0001 |
| Age, yrs (n = 25,253) | 56 ± 11 | 52 ± 10 | 53 ± 10 | 57 ± 10 | 61 ± 10 | 63 ± 10 | 64 ± 10 | 66 ± 9 | 68 ± 10 | <0.0001 |
| Male gender (n = 13,659) | 54% | 52% | 56% | 54% | 56% | 59% | 57% | 58% | 59% | <0.0001 |
| Ethnicity | | | | | | | | | | <0.0001 |
| Caucasian (n = 11,776) | 77% | 72% | 77% | 77% | 83% | 81% | 83% | 83% | 83% | |
| Hispanic (n = 1,334) | 9% | 11% | 9% | 9% | 6% | 6% | 7% | 6% | 4% | |
| African American (n = 637) | 4% | 5% | 5% | 4% | 3% | 4% | 3% | 3% | 4% | |
| Asian (n = 1,065) | 7% | 9% | 6% | 6% | 6% | 6% | 6% | 5% | 6% | |
| Other (n = 237) | 2% | 2% | 2% | 2% | 1% | 2% | 1% | 1% | 2% | |
| Asian Indian (n = 248) | 2% | 2% | 2% | 2% | 2% | 1% | 0.5% | 1% | 1% | |
| American Indian (n = 13) | 0.1% | 0.1% | 0.1% | 0.0% | 0.1% | 0.2% | 0.2% | 0.0% | 0.0% | |
| Native Hawaiian (n = 4) | 0.0% | 0.1% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | |
| Hypertension (n = 3,659) | 15% | 20% | 29% | 32% | 39% | 38% | 43% | 44% | 45% | <0.0001 |
| Diabetes mellitus (n = 961) | 4% | 4% | 6% | 8% | 10% | 11% | 14% | 16% | 18% | <0.0001 |
| Hyperlipidemia (n = 11,275) | 18% | 32% | 40% | 44% | 45% | 45% | 45% | 53% | 45% | <0.0001 |
| Total cholesterol (mg/dl) | | | | | | | | | | <0.0001 |
| <200 | 6% | 16% | 13% | 13% | 13% | 11% | 11% | 14% | 16% | |
| 201–240 | 10% | 24% | 25% | 23% | 22% | 22% | 22% | 16% | 18% | |
| 241–260 | 3% | 8% | 9% | 8% | 7% | 7% | 7% | 5% | 4% | |
| >260 | 3% | 7% | 6% | 6% | 5% | 6% | 4% | 4% | 2% | |
| On statin treatment | 9% | 11% | 18% | 22% | 26% | 23% | 27% | 34% | 31% | <0.0001 |
| Family history of premature CAD (n = 7,015) | 58% | 59% | 58% | 56% | 59% | 58% | 58% | 63% | 60% | 0.052 |
| Current smoker (n = 12,457) | 9% | 8% | 9% | 10% | 10% | 13% | 12% | 11% | 10% | <0.0001 |

Data are presented as whole percentages except when <1%, where data are presented to the tenth of a percent.
CAC = coronary artery calcium; CAD = coronary artery disease.

To understand to what extent longer-term outcomes from the current data series relates to near-term outcome, we performed a comparative analysis of the variability in long-term survival as compared with previous reports on near term (i.e., 5-year) in the report by Shaw et al. (8). This modeling was accomplished by pooling the datasets to include the total CAC score as well as other cardiac risk factors. A stratified Cox proportional hazards model was used to plot survival for the Shaw series and the current data set. This was done to examine how longer-term outcome would further define risk in asymptomatic individuals. It was our contention that the observation of 10 years might provide a closer approximation to longer-term outcome data available from other asymptomatic cohort studies, such as the Framingham study (7).

We also performed a post hoc sample size calculation for the comparison of survival rates across CAC scores. The calculations demonstrated that the available sample size of 25,253 patients was sufficiently large with a beta ≥0.80 and alpha = 0.01 to detect mortality differences between patients with CAC scores of 0, 1 to 10, 11 to 100, 101 to 400, 401 to 1,000, and >1,000, respectively (SamplePower, version 2.0, SPSS Inc., Chicago, Illinois).

Finally, we evaluated the prevalence of CAC in this clinical registry as compared with other population estimates, including data from MESA (Multi-Ethnic Study of Atherosclerosis) and CARDIA (Coronary Artery Risk Development In Young Adults Study) as well as the Nashville and Torrance clinical registries with meta-analytic techniques on the prevalence of detectable coronary calcium. The frequency of calcium in each of the cohorts was compared with Comprehensive Meta-Analysis software (Biostat, Englewood, New Jersey) with a random effects model.

## Results

**Clinical characteristics.** Of the 25,253 patients, the average age was 56 ± 11 years with nearly one-half being male and having a family history of premature coronary artery disease (CAD). The prevalence of cardiac risk factors was as follows: family history of premature CAD (58%), hypercholesterolemia (18%), hypertension (15%), smoking (9%), and diabetes (4%). In the overall cohort, the average CAC score was 146 ± 443 (Table 1).

In subsets with more extensive CAC scores, patients were older and had more frequent cardiac risk factors. Nearly one-half of the patients with CAC scores ≥1,000 were male ($p < 0.0001$), hypertensive ($p < 0.0001$), hyperlipidemic ($p < 0.0001$), or had a family history of premature CAD ($p = 0.052$).

**CAC scores.** More than one-half of patients had detectable CAC (i.e., CAC >0). Detectable CAC was most common in the left anterior descending and left circumflex coronary arteries. By comparison, 11.9% and 35.0% of patients had detectable CAC in the left main and right coronary arteries (Table 2).

**Table 2 Prevalence of CAC Scores by Vascular Territory**

| | Prevalence of CAC (%) |
|---|---|
| Total score | 57.3% |
| Vascular territory score | |
| Left anterior descending | 54.5% |
| Left main | 11.9% |
| Right coronary artery | 35.0% |
| Circumflex | 46.6% |
| Vascular territory—number of lesions | |
| Left anterior descending | 3.4 ± 3.8 (0–99) |
| Left main | 0.3 ± 0.9 (0–30) |
| Right coronary artery | 3.9 ± 5.3 (0–69) |
| Circumflex | 1.8 ± 2.8 (0–34) |
| Average score/lesion | |
| Left anterior descending | 30 ± 55 (0–1,566) |
| Left main | 6 ± 24 (0–580) |
| Right coronary artery | 15 ± 45 (0–1,860) |
| Circumflex | 12 ± 34 (0–988) |

CAC = coronary artery calcium.

For patients with detectable calcium, the average number of lesions was 3.4 and 3.9 in the left anterior descending and right coronary arteries. Similarly, for patients with detectable calcium, the average score/lesion ranged from 6 for a left main lesion to 30 for a left anterior descending coronary artery.

**Univariable clinical risk factor and CAC predictors of death.** Significant clinical predictors of death included age, diabetes, smoking, male gender, hypertension, and family history of premature CAD (all $p < 0.0001$). The relative RRs for these cardiac risk factors ranged from 1.1 (95% CI 1.09 to 1.11)/decade of increasing age to 3.86 (95% CI 3.03 to 4.92) for diabetes (both $p < 0.0001$). The RR for family history of premature CAD was 0.63 (95% CI 0.51 to 0.78) in large part because those referred for evaluation were younger ($p < 0.0001$) (Table 3).

**Cumulative long-term survival of CAC scores.** Survival varied significantly by the extent of CAC ($p < 0.0001$) (Fig. 1A). Unadjusted survival was 99.6%, 99.1%, 97.4%, 93.5%, 89.5%, 87.5%, 83.4%, and 73%, respectively, for CAC scores of 0, 1 to 10, 11 to 100, 101 to 399, 400 to 699, 700 to 999, and ≥1,000 ($p < 0.0001$). After adjustment for risk factors, including age, in patients with CAC scores of 0, 1 to 10, 11 to 100, 101 to 399, 400 to 699, 700 to 999, and ≥1,000, 10-year survival was 99.4%, 99.3%, 98.1%, 96.6%, 94.7%, 93.9%, 92.4%, and 87.8%, respectively ($p < 0.0001$) (Fig. 1A).

When compared with the 11,044 patients with no calcium, scores of 1 to 10, 11 to 100, 101 to 399, 400 to 699, 700 to 999, and ≥1,000 showed RR of 2.56 (95% CI 1.54 to 4.27), 6.73 (95% CI 4.58 to 9.87), 12.83 (95% CI 8.71 to 18.91), 23.17 (95% CI 14.31 to 37.52), 27.58 (95% CI 18.19 to 41.80), 36.43 (95% CI 23.21 to 57.19), and 62.58 (95% CI 43.04 to 91.00), respectively ($p < 0.0001$). The CAC remained highly significant ($p < 0.0001$) in a multivariable model controlling for age, gender, ethnicity, diabe-

**Table 3 Univariable Predictors of Death From All Causes—in Reverse Order by Chi-Square Value**

| | Relative Risk | 95% CI | Chi-Square | p Value |
|---|---|---|---|---|
| Clinical history | | | | |
| Age (/decade) | 1.10 | 1.09–1.11 | 585 | <0.0001 |
| Diabetes | 3.86 | 3.03–4.92 | 137 | <0.0001 |
| Smoking | 3.10 | 2.43–3.95 | 92 | <0.0001 |
| Male gender | 2.08 | 1.72–2.52 | 59 | <0.0001 |
| Hypertension | 1.73 | 1.40–2.14 | 26 | <0.0001 |
| Family history of premature CAD | 0.63 | 0.51–0.78 | 19 | <0.0001 |
| Hyperlipidemia | 0.90 | 0.70–1.16 | 1 | 0.42 |
| Coronary calcium results | | | | |
| CAC score categories of 1–10, 11–100, 101–299, 300–399, 400–699, 700–999, ≥1,000 vs. 0 | 1.68 | 1.63–1.74 | 1,181 | <0.0001 |
| Lesions | | | | |
| LM | 1.31 | 1.27–1.35 | 560 | <0.0001 |
| Circumflex | 1.15 | 1.13–1.18 | 209 | <0.0001 |
| RCA | 1.07 | 1.06–1.08 | 186 | <0.0001 |
| LAD | 1.06 | 1.05–1.07 | 156 | <0.0001 |
| Score | | | | |
| LM | 2.19 | 1.99–2.41 | 326 | <0.0001 |
| LAD | 1.68 | 1.57–1.81 | 238 | <0.0001 |
| Circumflex | 1.61 | 1.52–1.71 | 279 | <0.0001 |
| RCA | 1.56 | 1.46–1.67 | 174 | <0.0001 |
| Average lesion extent | | | | |
| LM | 1.01 | 1.008–1.011 | 401 | <0.0001 |
| LAD | 1.003 | 1.003–1.004 | 256 | <0.0001 |
| Circumflex | 1.005 | 1.004–1.006 | 256 | <0.0001 |
| RCA | 1.003 | 1.002–1.004 | 225 | <0.0001 |
| CAD extent (/vessel) | 2.69 | 2.35–3.08 | 270 | <0.0001 |

Description of CAC univariable models: 1) CAC score categories of 1–10, 11–100, 101–299, 300–399, 400–699, 700–999, ≥1,000 vs. 0: This model provides a univariable risk ratio for each category of increasing CAC extent (n = 7 categories) as compared with a CAC score of 0. Individual risk ratio were not analyzed, because additional analyses within the results provides risk-adjusted risk ratios. 2) For the LM, circumflex, RCA, and LAD lesions, this is an analysis of the total number of lesions within each vascular territory; as such, the risk ratio reveals the increase for every number of lesions when compared with no lesions in that vascular territory. 3) For the average lesion extent univariable analysis, this examines the average vascular territory score/lesion identified within the LM, circumflex, RCA, and LAD areas. Thus, the risk ratio reveals the *x*-fold increase in mortality for a given average lesion extent. 4) The CAD extent analysis includes the number of vascular territories with scores ≥100.

CAC = coronary artery calcium; CAD = coronary artery disease; CI = confidence interval; LAD = left anterior descending territory; LM = left main territory; RCA = right coronary artery territory.

tes, hyperlipidemia, hypertension, as well as other cardiac risk factors listed in Table 1. However, in the risk-adjusted model, the statistical difference between a CAC score of 0 vs. 1 to 10 was no longer significant ($p = 0.29$).

When grouped by the number of vascular territories with CAC scores of ≥100, a measure of atherosclerotic disease extent, survival varied significantly for patients with no vessel involvement as compared with 1 to 3 vessel CAC disease. For patients with CAC <100, unadjusted survival at 12 years was 98.8% as compared with survival rates of 90.4% (RR 3.81, 95% CI 2.63 to 5.53), 83.8% (RR 6.38, 95% CI 3.59 to 11.34), 78.0% (RR 8.41, 95% CI 2.70 to 6.19), and 74.8% (RR 10.26, 95% CI 6.46 to 6.28), respectively, for patients with 1, 2, and 3 vessel CAC and left main disease ($p < 0.0001$). After adjustment for risk factors including age, the survival at 12 years was 98.2% for patients with a CAC score <100 as compared with survival rates of 97.1%, 95.7%, and 94.6%, respectively, for patients with 1, 2, and 3 vessel CAC and left main disease ($p < 0.0001$) (Fig. 1B).

We further evaluated the long-term survival in patients with single vessel CAC scores ranging from 11 to 100 (Fig. 1C) Twelve-year unadjusted survival ranged from 99.4% for no vessel involvement to 84.7% for patients with 3 vessels with scores of 11 to 100 ($p < 0.0001$). Risk-adjusted survival for patients with CAC scores from 11 to 100 is plotted in Figure 1C ($p < 0.0001$). The ensuing risk-adjusted RR was elevated 1.66-fold ($p = 0.031$) and 1.84-fold ($p = 0.003$) for patients with 3 vessel and 3 vessel plus left main CAC scores from 11 to 100 as compared with CAC score <11 in any of the major epicardial coronary arteries.

**Comparative analysis of 5- and 12-year survival from 2 databases.** Previous reports have limited follow-up from 3 to 5 years of observation (8). To compare near- and long-term outcome by CAC scores, we examined unadjusted and risk-adjusted survival in cohorts from Nashville, Tennessee (n = 10,377) and Los Angeles, California (n = 25,253) (Fig. 2). There were no differences in prevalence of CAC in each cohort ($p = 0.88$) (Table 4). Cumulative survival at 5 years ranged from 99.4% to 81.8% for patients

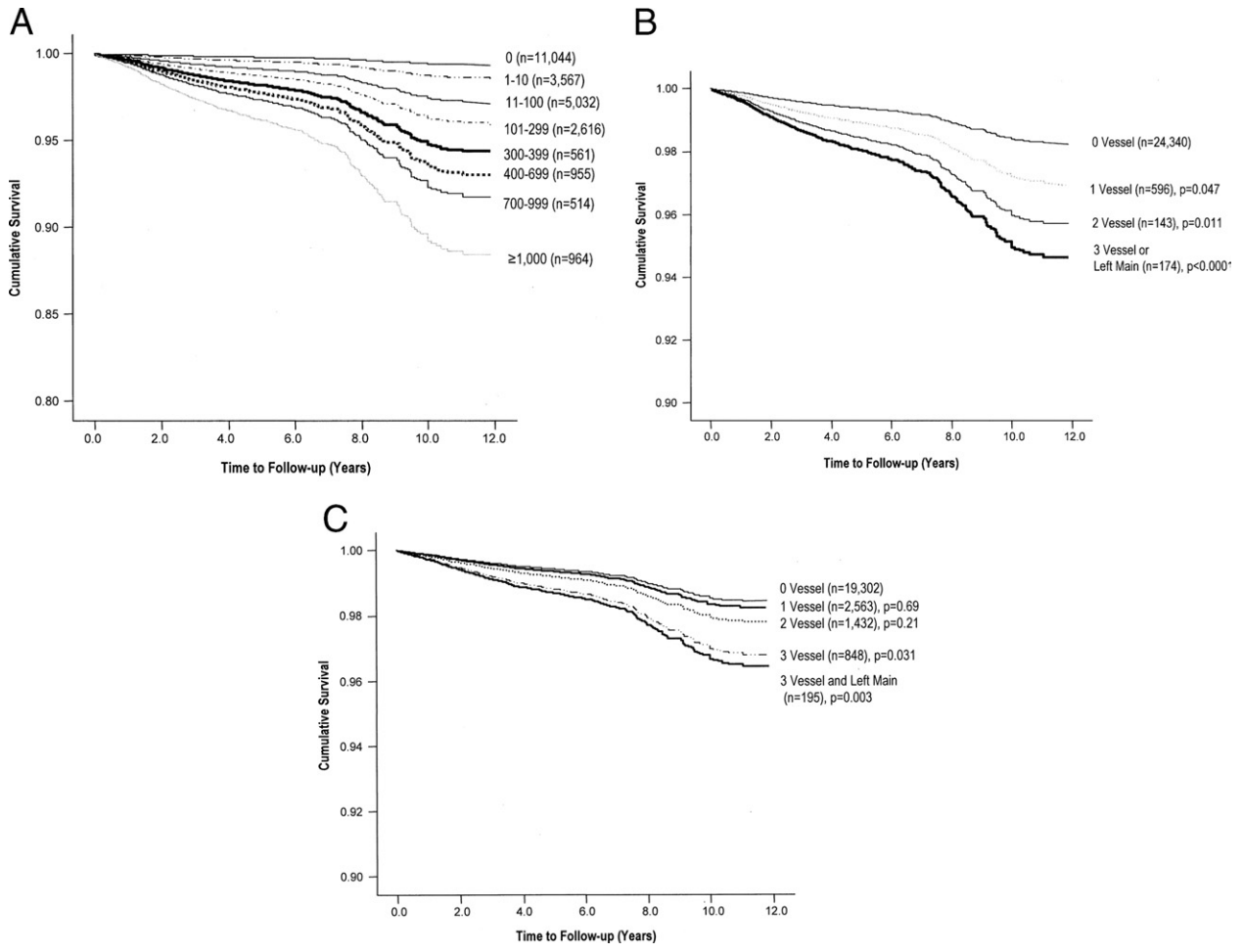


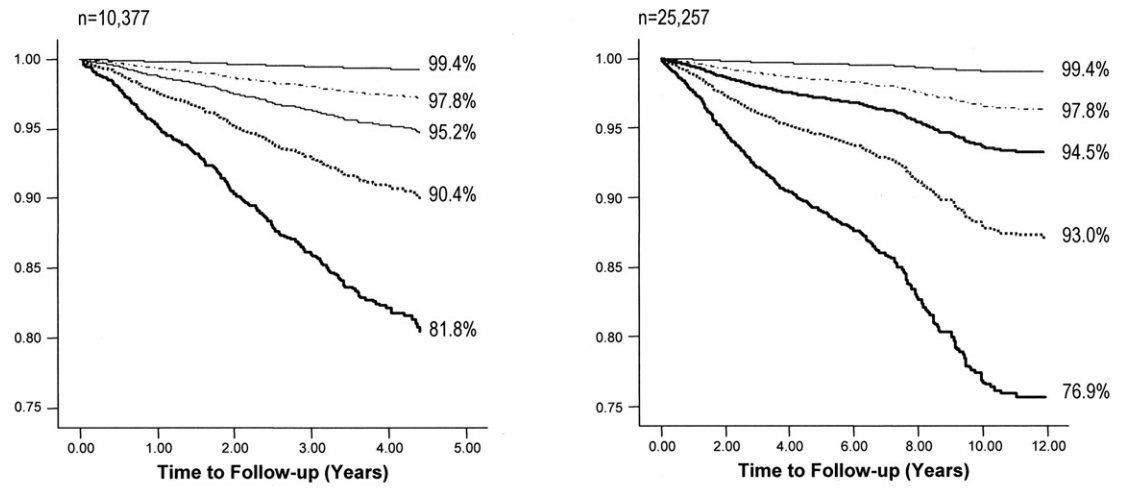

**Figure 1** **Risk-Adjusted Cumulative Survival by CAC Score**

Risk adjustment included the following variables: age, hypercholesterolemia, diabetes, smoking, hypertension, and a family history of premature coronary heart disease. **(A)** Subsets ranging from 0 to ≥1,000. The increasing calcium scores were associated with worsening survival. Each increment of calcium score was associated with significant increased risk of all-cause mortality (chi-square = 1,363, $p < 0.0001$ for variable overall and for each category subset). Model chi square = 2,017, $p < 0.0001$, and chi-square = 274 for variable ($p < 0.0001$ overall and for each category subset). Scale on this curve is from 0.80 to 1.00, whereas the remaining curves are plotted within a range of 0.90 to 1.00. **(B)** Cumulative survival by the coronary calcium extent in the number of vascular territories with scores ≥100, adjusted for age and risk factors. There was worsening survival with increasing number of calcified vessels (chi-square = 251, $p < 0.0001$). Model chi-square = 1,290, $p < 0.0001$, and chi-square = 27 for variable ($p < 0.0001$ overall and p value for each category subset is stated in figure). The survival curve for 3 vessel (n = 28) was superimposed on the left main subset and, for that reason, the 2 were combined to form 1 category. **(C)** Cumulative survival in patients with coronary artery calcium (CAC) scores in the range of 11 to 100. Even in patients with small amounts of CAC, increasing number of vessels involved was associated with worsening long-term survival (chi-square = 182, $p < 0.0001$ for the variable and for each category subset). Model chi-square = 1,148, $p < 0.0001$, and chi-square = 13 for variable ($p = 0.013$ overall and p value for each category subset is stated in figure).

with CAC scores of 0 to 10 to >1,000 ($p < 0.0001$). In a stratified Cox model with follow-up up to 5 years after imaging, survival was similar between the 2 cohorts for patients with a CAC score 0 to 10, 11 to 100, 101 to 400, 401 to 1,000, and >1,000 (all $p > 0.90$). By 12 years of follow-up, cumulative survival rates were 99.4%, 97.8%, 94.5%, 93.0%, and 76.9% for patients with CAC scores of 0 to 10, 11 to 100, 101 to 400, 401 to 1,000, and >1,000, respectively ($p < 0.0001$). Risk of mortality for each score category increased with increasing score. In comparing survival rates between the Nashville, Tennessee and Torrance, California databases, mortality increased from 0.7% ($p = 0.0073$) to 4.9% ($p < 0.0001$) for more extended follow-up from the Torrance registry; even in risk-adjusted models that controlled for age, gender, hypertension, hyperlipidemia, and diabetes (Fig. 2).

**Risk-adjusted models.** In several risk-adjusted models (Table 5), CAC scores remained independently predictive of all-cause mortality even after adjusting for age, gender, ethnicity, hypertension, hyperlipidemia, diabetes, smoking, and family history of premature CAD.

**Added value of CAC versus traditional risk factors.** With the CAC score, the C-index defined from a ROC curve was 0.813 (95% CI 0.794 to 0.832), significantly




| CAC Score | (5 Yr Mortality = 1.2%) | (12-Yr Mortality = 2.1%) | Difference |
|---|---|---|---|
| 0-10 | 99.4% | 99.4% | 0.0% |
| 11-100 | 97.8% | 97.8% | 0.0% |
| 101-400 | 95.2% | 94.5% | 0.7% |
| 401-1,000 | 90.4% | 93.0% | 0.6% |
| >1,000 | 81.8% | 76.9% | 4.9% |

**Figure 2** **Near- and Long-Term Survival From 2 EBT Centers: Nashville, Tennessee, and Los Angeles, California**

Comparison of 5-year mortality rates in 2 different cohorts. The results are quite consistent across different study groups (chi-square = 1,503, $p < 0.0001$, interaction $p < 0.0001$). CAC = coronary artery calcium; EBT = electron beam tomography.

higher than that observed for a model of the number of cardiac risk factors (C-index = 0.611; 95% CI 0.585 to 0.637) (Fig. 3A). Of the available risk factor data (see Fig. 3B), age provided the best discrimination in mortality with CAC providing additional statistical information ($p < 0.0001$).

Table 5 includes C-indexes from multivariable models. In these risk-adjusted models, the CAC scores remained independently predictive of mortality even when applying categorical or vascular territory scores (Table 5). Additionally, the % information content ranged from 4% to 14% for the CAC score when considering all other traditional risk factors.

## Discussion

This cohort represents the largest and longest follow-up after scanning for CAC. This long-term follow-up reveals that coronary calcium scores >10 are predictive of an increased risk, potentially reducing the threshold for instituting aggressive medical therapy (e.g., statins, aspirin). The end point, all-cause mortality, with over 500 events, provides this investigation with sufficient statistical power (beta ≥0.80) to evaluate the prognostic significance of CAC. The results are concordant with other similar studies, demonstrating that increasing plaque burden is associated with increasing risk. Earlier reports on this modality were based on highly selected cohorts with the numbers of end points often being quite low. This study, similar to the study by Shaw et al. (8), used all-cause mortality as a more definitive end point. All-cause mortality is not subject to misclassification of the cause of death on physician's reports (9). Furthermore, in the U.S., atherosclerosis accounts for a sizeable proportion of deaths, and more so in a population at-risk for the disease (10). Thus, our analysis that was conducted, with established epidemiologic methods in a sufficiently large population, showed that the extent of CAC is highly correlated with mortality risk. The present study, a large cohort with long follow-up, provides supportive evidence that there is a linear relationship between the extent of CAC and all-cause mortality.

The calcium score also added incremental value to variables contained within the Framingham risk model. When CAC scores were added to risk factors in patients in the study by Shaw et al. (8), the estimation of risk increased vis-à-vis a significant improvement in the C-index ($p <$

**Table 4** **Prevalence of CAC by Dataset**

| | Nashville | Harbor-UCLA |
|---|---|---|
| 0–10 | 57% | 58% |
| 11–100 | 20% | 20% |
| 101–400 | 14% | 13% |
| 401–1,000 | 6% | 6% |
| >1,000 | 3% | 4% |

Chi-square linear p trend, p = 0.88.
CAC = coronary artery calcium.

**Table 5** Risk-Adjusted Models for All-Cause Death

| | Relative Risk | 95% CI | % of Chi-Square | p Value | C-Index* |
|---|---|---|---|---|---|
| Model† 1: CAC score | | | | | |
| Overall | 1.31 | 1.23–1.39 | 14% (274/2,017) | <0.0001 | 0.757 (0.728–0.787) |
| 1–10 | 1.48 | 0.71–3.07 | | 0.29 | |
| 11–100 | 3.61 | 2.11–6.18 | | <0.0001 | |
| 101–399* | 3.84 | 2.20–6.68 | | <0.0001 | |
| 400–699 | 5.78 | 3.00–11.16 | | <0.0001 | |
| 700–999 | 6.47 | 3.37–12.43 | | <0.0001 | |
| ≥1,000 | 9.36 | 5.36–16.33 | | <0.0001 | |
| Model† 2: CAD extent (/vessel) | | | | | |
| Overall | 1.58 | 1.28–1.96 | 4% (25/677) | <0.0001 | 0.552 (0.511–0.592) |
| 1-vessel | 1.39 | 0.95–2.03 | | 0.086 | |
| 2-vessel | 1.85 | 1.03–3.30 | | 0.038 | |
| 3-vessel or left main | 2.44 | 1.58–3.78 | | <0.0001 | |

*For this risk-adjusted model, survival was similar for categories of 101–299 and 300–399 and were collapsed for this analysis. †Risk-adjusted controlling for age, gender, hypertension, hyperlipidemia, diabetes, family history of premature coronary disease, smoking, and ethnicity. C-index for risk factor data = 0.354 (0.312–0.395). The C-indexes for CAC were significantly greater than classification by risk factor data ($p < 0.0001$ for model 1 and $p = 0.008$ for model 2).

Abbreviations as in Table 3.

0.001). In our analyses with an array of univariable and multivariable methodologies, C-indexes consistently improved after the addition of CAC measures to risk factor models ($p < 0.0001$). The C-index and odds ratio similarly increased in other large studies of CAC. A study by Raggi et al. (11) demonstrated odds ratios of 21.5 for future hard cardiovascular events for patients in the highest quartile of calcium scores. That correlates well with this study, in which a score of 300 to 399 was associated with an RR of 23, and score of 400 to 699 with an RR of 27, as compared with patients without CAC. In the St. Francis Heart Study (12), in which over 4,900 patients were followed for 4.3 years, a score >400 was associated with a 30-fold increased risk for CAD death or myocardial infarction. From this report by Arad et al., the CAC score predicted CAD events more accurately than the Framingham risk index. The area under the ROC curve was 0.79 ± 0.03 for the calcium score versus 0.68 ± 0.03 for the Framingham index ($p < 0.0006$). In the recently reported Prospective Army Coronary Calcium Project, in which younger patients were evaluated with EBT and followed prospectively, CAC was associated with a 12-fold increased risk for hard CHD events ($p = 0.004$) even after controlling for the Framingham risk score (13).

In the current study, patients with CAC scores ≥1,000 had a very high risk of all-cause mortality. This parallels the incidence of hard cardiac events demonstrated by Wayhs et al. (14), in which patients with CAC scores >1,000 had a 25% 1-year event rate. A recent study also demonstrated risk stratification in 510 uncomplicated type-2 diabetic patients prospectively enrolled and undergoing CAC (15).

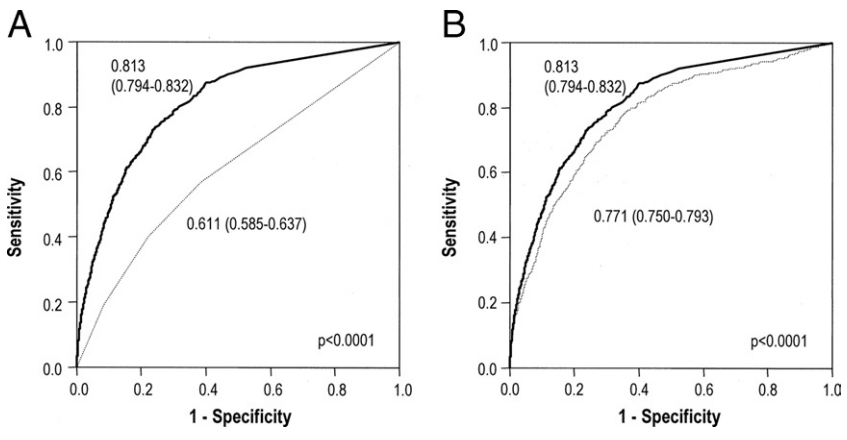



**Figure 3** Receiver-Operating Characteristic Curves Noting the Incremental Value of the Total Agatston Scores Over and Above the Total Number of Clinical Risk Factors as Well as Age

These curves note the available data revealing the highest area under the curve for clinical risk factors. In both cases, the addition of the Agatston score resulted in a significant improvement in the area under the curve ($p < 0.0001$ for the total number of risk factors **[A]** and for age **[B]**). Receiver-operating characteristic analysis for other individual risk factors were <0.586 for gender, 0.440 for family history, 0.573 for smoking, 0.577 for diabetes, 0.518 for ethnicity, 0.484 for hyperlipidemia, and 0.562 for hypertension.

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The ROC analysis demonstrated that CAC predicted cardiovascular events with the best area under the curve (0.92), significantly better than the United Kingdom Prospective Diabetes Study Risk Score (0.74) and Framingham Score (0.60) ($p < 0.0001$). The RR to predict a cardiovascular event for a CAC score of 101 to 400 was 10.1 and increased to 58.1 for scores >1,000 ($p < 0.0001$). Our cohort similarly demonstrated unadjusted relative risks from 12.8 to 62.6 for similar CAC groups.

Patients without evidence of CAC in this study experienced a very low event rate, with 12-year survival of 99.4%. This low event rate in patients without CAC has been observed in other studies. Arad et al. (12) demonstrated an annual event rate of 0.1%, Taylor et al. (13) demonstrated an event rate of 0.06%, and Raggi et al. (11) demonstrated an annual event rate of 0.11% for persons with no detectable CAC by EBT. Indeed, even a cohort of approximately 900 diabetic patients followed for 5-year survival was 98.8% in the absence of CAC (16). In that study, diabetic and non-diabetic patients with no CAC demonstrated a similar survival (98.8% and 99.4%, respectively, $p = 0.5$). In a prospective study of type-2 diabetic patients, no cardiac events or perfusion abnormalities occurred in subjects with a CAC score ≤10 through 2 years of follow-up (15). The only study reporting a higher event rate for 0 scores used atypical image acquisition and quantification of CAC, relying on thick slices (6 mm) and large areas of calcification (17), which has been shown to result in data loss (18).

The low risk associated with a 0 score provides further evidence that these patients, despite some high risk attributes, might be at sufficiently low risk to recommend against cholesterol-lowering drug therapy (given the cost) and aspirin therapy (given the risk of hemorrhagic stroke associated with aspirin use) (2). Conversely, a score higher than 100 might lead to the recommendation of continued aspirin use and more aggressive lipid control aiming for a goal low-density lipoprotein-C level of <100 mg/dl, as suggested currently by the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III): "In persons with multiple risk factors, high coronary calcium scores (e.g., >75th percentile for age and gender) denote advanced coronary atherosclerosis and provide a rationale for intensified low-density lipoprotein–lowering therapy" (19). Current recommendations are to use cardiac computed tomography for measuring CAC in individuals determined to be at intermediate clinical risk according to the NCEP-ATP III criteria and in whom decisions concerning prevention strategies might be altered on the basis of the test results (20).

**Study limitations.** Although the current article includes a rigorous analysis of the prognostic value of CAC, the majority of patients referred for calcium scanning had cardiac risk factors and, as such, are not representative of the general population. We had incomplete information related to cardiovascular risk factors, because these measures were taken by survey rather than being measured. The prevalence of hypercholesterolemia, hypertension, and diabetes in our population was similar to that observed in other large, population-based studies of CHD (21) and in studies on CAC and CHD (7,22–24). Recent large epidemiologic studies (NIH-NHLBI MESA and CARDIA) (25) demonstrate similar prevalence rates for CAC compared with our cohort (Fig. 4). Thus, results from the current cohort seem similar to population-based estimates of atherosclerosis.

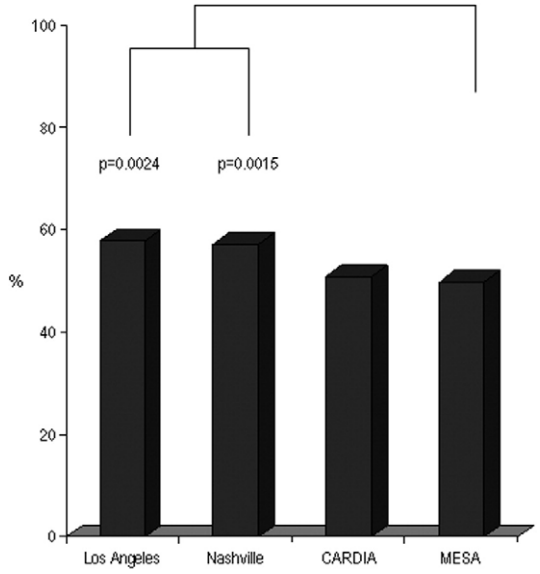


**Figure 4** **Comparative Analysis of Population Sample Prevalence Rates for Coronary Calcification**

This study (Los Angeles) demonstrates similar prevalence to the prior all-cause mortality study from Nashville, Tennessee, and only slightly greater prevalence than the CARDIA (Coronary Artery Risk Development In Young Adults) study and MESA (NIH-NHLBI Multi-Ethnic Study of Atherosclerosis).

Previous studies have demonstrated a sensitivity of 98% and a specificity of 99% for self-reported hypertension as compared with measured values (26). We expect that our well-educated population would similarly fall into these levels of precision. It is expected that the inclusion of measured risk factors, such as systolic blood pressure, blood glucose level, and cholesterol values, would provide a better estimation of risk than historical data alone. However, the use of categorical risk factors instead of continuous variables has been shown to constitute a valid approach to risk assessment (27). Hence, we believe that a risk assessment approach on the basis of historical risk factors rather than on continuous variables does not significantly weaken the assumptions made in this study.

We observed a decrement in predictive capabilities for risk factor models (i.e., the C-index was lower for categorical risk factors as compared with the CAC score), including family history of premature disease, smoking, and diabetes. The reduced C-indexes for traditional cardiac risk factors, we believe, are the result of concurrent treatment for

hypertension, diabetes, and hypertension as well as a younger age for screening patients with a family history of premature coronary disease. However, use of categorical risk factors results in an underestimation in their predictive abilities. Despite this limitation, the availability of categorical risk factor data is consistent with current clinical practice where physicians are generally limited by the availability of only partial, self-reported, categorical data. Therefore, there is a possibility that the value of CAC testing is being overinflated when measured with observed risk factors, as compared with measured risk factors.

Information on subsequent therapy after calcium scanning is unknown. We have previously demonstrated that patients with higher calcium burdens are more likely to be placed on statin therapy and more likely to maintain statin therapy (improved adherence) over the subsequent 3 to 5 years (28). Thus, higher calcium scores are confounded by improved anti-atherosclerotic therapies that would possibly lower cardiovascular mortality. However, this confounder would weaken the predictive value of coronary calcification.

Additionally, the National Death Index data do not include the cause of death and, as such, our models include mortality possibly unrelated to atherosclerotic disease. However, the bias resulting from death misclassification does not occur in all-cause mortality models, and in this age group, the prevalence of CHD deaths has been reported to be approximately one-third of death from all-causes (29). If two-thirds of deaths in the American population are unrelated to coronary disease risk factors, it is possible that the addition of standard CAD risk factors to age would reduce the accuracy of the predictive model for all-cause mortality. However, the cardiovascular death rate, in a patient population referred with cardiovascular risk factors, should be much higher than general population estimates. Patients with active cancer, acquired immune deficiency syndrome, congestive heart failure, or advanced lung disease were generally not referred for calcium scoring to assess cardiovascular risk.

## Conclusions

We collected mortality data on 25,253 consecutive, asymptomatic individuals referred by primary care physicians for CAC scanning. This large observational data series strongly indicates that CAC is an independent estimator of all-cause mortality. Our results reveal a marked difference in survival at 6.8 years as the CAC scores increase from 0 to >1,000. This supports the notion that increasing coronary atherosclerosis is a strong and independent predictor of future cardiac events. Furthermore, our study shows that CAC provides independent and incremental prognostic information in addition to traditional risk factors in the prediction of all-cause mortality.

**Reprint requests and correspondence:** Dr. Matthew J. Budoff, Harbor-UCLA Research and Education Institute, 1124 West Carson Street, RB2, Torrance, California 90502. E-mail: mbudoff@labiomed.org.

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